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Treatment of Bacterial Meningitis with Penicillin, Sulfonamides, and Sera*

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BACTERIAL meningitis before the era of specific therapy was a highly lethal disease regardless of etiology. The mortality due to meningococcic meningitis was variously reported as from 20 to 90 per cent,[6] more generally nearer the latter figure. Pneumococcic, streptococcic and staphyococcic meningitis were almost uniformly fatal.[6] Only rare patients recovered from influenzal meningitis.[1]

Serum and antitoxin therapy probably reduced the mortality of meningococcic disease,[6] although this fact is difficult to demonstrate statistically.

The advent of sulfonamide drugs significantly altered the picture, particularly as regards meningococcic meningitis,[4,5,7,10] but to a lesser extent in the pneumococcic, streptococcic, staphylococcic,[6] and H. influenzae[1] infections of the meninges. More recently, penicillin has been introduced as a therapeutic agent for the treatment of meningitis.

The exact role played by the various sulfonamides, penicillin, and sera in treatment has not yet been defined. Hence the physician is in the fortunate position of having at his command several potent weapons, but he is in the dilemma of having to choose from amongst them the ideal treatment for each individual patient.

The purpose of this paper is to compare the relative efficacy of the several modes of treatment of various kinds of meningitis, and, after studying the effect of certain prognostic factors on the mortality of meningococcic and pneumococcic meningitis, to formulate a plan of therapy for each type of meningeal infection. In addition, several examples of unusual types of meningitis are reported.

A discussion of the diagnosis of meningitis is not warranted here. However, an early etiologic diagnosis is of paramount importance, and every effort must be made to isolate the invading organism, so that treatment may be directed to best advantage.

TREATMENT

Two hundred and sixty-five cases of bacterial meningitis were admitted to the Isolation Division of the San Francisco Hospital during the period January, 1943, to February, 1946 (Table 1). Of these, 14 were tuberculous and received no specific treatment. All other patients received sulfonamide drugs, penicillin, sera, or combinations of these

TABLE 1.—*Incidence and Mortality of Bacterial Meningitis.*

Etiology	Number	Gross Mortality Per Cent	*Corrected Mortality Per Cent
N. meningococcus	182	20.3	11.5
D. pneumoniae	40	67.5	60.6
M. tuberculosis	14	100.0	...
H. influenzae	7	14.1	...
Staphylococcus aureus	4	0.0	...
Staphylococcus albus	4	50.0	33.3
Streptococcus hemolyticus	3	33.3	...
Streptococcus viridans	2	100.0	...
Aerobacter aerogenes	2	50.0	0.0
E. coli	3	0.0	...
N. flava	1	0.0	...
N. catarrhalis	1	100.0	...
Listerella monocytogenes	1	100.0	...
T. pallidum	1	100.0	...
Total	265	...	...

*Mortality corrected for patients surviving less than 24 hours.

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agents. No attempt was made to treat alternate patients by different methods, but rather the therapeutic regime was changed as each new agent became available and as our experience advanced. During 1943, cerebrospinal fever was epidemic in San Francisco and cases exhibited much more severe degrees of involvement than previously. In the succeeding years, both the incidence and virulence were somewhat above the average level. Patients treated at the San Francisco Hospital come principally from war-crowded sections and lower economic groups. The incidence of alcoholism and pre-existing disease is relatively high.

During this three-year period, sulfadiazine and sulfamerazine have been used to the exclusion of other sulfonamides because of their high degree of effectiveness and comparatively low toxicity. Before the introduction of penicillin, occasional patients manifesting renal irritation due to one or the other newer sulfonamide were shifted to sulfanilamide with uniform success. In all except the mildest cases, the initial dose of sulfonamide was given parenterally in the form of the sodium salt dissolved in physiologic saline solution or one-sixth molar lactate solution. The initial dose was 5 Gm. for adults and approximately 20 mg. per pound of body weight for children. Parenteral medication was continued until the patient was able to take the drug orally. If continued intravenous or subcutaneous medication was necessary, 3 Gm. were administered to adults every eight hours in the instance of sodium sulfadiazine, or every ten to twelve hours in the case of sodium sulfamerazine. The dosage for children was calculated to furnish 60 mg. per pound of body weight per 24 hours.

Blood sulfonamide determinations were done as required and an attempt was made to maintain the drug level in excess of 10 mg. per cent. Oral medication was instituted as soon as feasible, or, in instances of protracted coma, the drug and fluids, as well as a high caloric formula, were given by stomach tube. In adults, 1 to 1.5 Gm. were given every four hours (sulfadiazine) or every six hours (sulfamerazine). Occasional patients received sulfamerazine every eight hours, but it was found that slightly greater individual doses were usually required to produce the desired blood concentration. The oral dose in children was 60 to 90 mg. per pound of body weight, divided into four to six doses daily.

Alkalinization of the urine was accomplished by sufficient sodium bicarbonate by mouth or sodium lactate by vein or hypodermoclysis. Adequate fluids to insure a daily urinary output of at least 1,500 cc. were given to all patients. Blood counts were done every other day, and urine examinations were done daily. On this regime only one instance of severe sulfonamide intoxication was encountered, although microhematuria was not infrequent.

Sulfonamide medication was continued for two weeks in earlier cases of meningococcic meningitis, but this period was later reduced to one week and no instances of recurrence were encountered. In meningococcic meningitis the spinal fluid usually soon became sterile, although the clinical response did not necessarily run parallel. Sulfonamides were continued for at least two weeks in cases of pneumococcic, streptococcic, staphylococcic and influenzal meningitis.

The penicillin dosage varied widely. From 15,000 to 60,000 units were injected intramuscularly every three hours. A few patients received 50,000 units of penicillin in sesame oil and beeswax every eight hours. In addition, 10,000 units of penicillin dissolved in 10 cc. of saline were introduced intrathecally once daily until the spinal fluid became sterile and the sugar content reached normal levels. This rarely required more than three injections for patients who recovered. We feel that intrathecal medication is a necessary procedure, although in some instances, undoubtedly, intramuscular administration might suffice. Penicillin, intramuscularly, was continued for one week in meningococcic infections and for at least two weeks in other forms of coccic meningitis.

USE OF ANTISERUMS

Pneumococcus antiserum, when used, was given initially intravenously in a dose of 100,000 units and this was repeated at 12-hour intervals as required. Meningococcus antiserum and antitoxin were used only in a few cases in 1943 before this procedure was discontinued on the assumption that no extra benefit was derived.[4] Type B Hemophilus influenzae rabbit antiserum was administered intravenously only, according to the plan of Alexander and associates,[1] judging the dose and interval by the condition and age of the patient, the sterility and sugar content of the spinal fluid, and the ability of the patient's serum to produce capsular swelling of his own infecting organism. On clinical grounds we feel that capsular swelling by undiluted serum indicates adequate antibody content.

In addition, sedation was given as required with barbiturates, morphine, or paraldehyde. Plasma[4] and adrenal cortical hormone in large doses were administered in all instances of shock, although their effect was often disappointing. Lumbar punctures were repeated on the following indications: (1) introduction of penicillin, (2) lack of therapeutic response, (3) pressure symptoms and signs, and (4) doubt as to bacteriologic diagnosis.

Meningococcic meningitis responded equally well to sulfadiazine and sulfamerazine (Table 2). The mortality in patients treated with a combination of penicillin and sulfonamide was less than half that of patients treated with sulfonamides alone. The combined therapy group is still too small to draw

TABLE 2.—*Comparative Results in Meningococcic Meningitis with Various Forms of Therapy.*

(Cases Surviving Less Than 24 Hours Excluded)

Treatment	Number	Deaths	Mortality Per Cent
Sulfadiazine	77	9	11.7
Sulfamerazine	62	8	12.9
All Sulfonamides	139	17	12.2
Penicillin	1	0	0.0
Penicillin and Sulfonamides	21	1	4.8

final conclusions, but it is our clinical impression that the difference is probably significant. Only one patient was treated with penicillin alone, so we can offer no comment on the efficacy of this agent without sulfonamides, but Meads and associates[9] feel that penicillin is inferior to sulfadiazine in the treatment of cases of meningococcic meningitis because of slower clinical and bacteriologic response. and the occurrence of relatively penicillin-resistant strains of meningococci. Likewise White and associates[14] recognize the limitations of penicillin in cerebrospinal fever. On the other hand, Rosenberg and Arling[11] report 64 recoveries in 65 patients with meningococcic meningitis treated with penicillin alone.

We had hoped, after a discouraging experience with the sulfonamide treatment of cases of pneumococcic meningitis, that penicillin, used in addition, would reduce the mortality appreciably.[3,13] The fatality rate, however, was not significantly altered by combined penicillin and sulfadiazine therapy (Table 3). Appelbaum and Nelson,[2] in this respect, found that penicillin treatment following unsuccessful sulfonamide therapy, or used in conjunction with sulfonamides was still attended by a high mortality. The results of White and associates[14] also suggest that combined sulfonamide and penicillin, as well as penicillin alone, have not greatly lowered the fatality rate in cases of pneumococcic meningitis. Others[8,12] have obtained equal or better results with penicillin alone, but our experience in this regard is too limited to draw conclusions.

TABLE 3.—*Comparative Results in Pneumococcic Meningitis with Various Forms of Therapy.*

(Cases Surviving Less Than 24 Hours Excluded)

Treatment	Number	Deaths	Mortality Per Cent
Sulfadiazine	4	3	75.0
Sulfamerazine	5	3	60.0
All Sulfonamides	9	6	66.7
Penicillin	2	1	50.0
Penicillin and Sulfonamides	19	11	57.9
Sulfonamides and Serum	7	5	71.4

Results in a small group of patients suffering from H. influenzae meningitis were encouraging. All seven were treated with sulfonamides in high dosage, and all but one, whose organism could not be typed with available sera, received type B rabbit antiserum. Unusual difficulty in maintaining an adequate blood sulfonamide concentration was encountered several times. Six of the seven patients survived, including two under one year of age.

All three patients with beta hemolytic streptococcic meningitis were treated with penicillin. Two, who had mastoidectomies, survived. The fatal case also had generalized streptococcic peritonitis and died in spite of large amounts of penicillin and sulfonamides.

Two patients with streptococcus viridans meningitis were treated with sulfonamides because penicillin was unavailable, and both died.

One patient with staphylococcus albus meningitis treated with sulfadiazine alone expired. Of seven other patients with staphylococcic meningitis receiving penicillin, only one fulminant case of the Waterhouse-Friderichsen type died.

One patient infected with Aerobacter aerogenes died after a fulminant illness of less than 24 hours. One other Aerobacter aerogenes meningitis and two cases of E. coli meningitis were successfully treated with sulfadiazine. In addition, one patient whose meninges were infected with a paracolon bacillus, survived after treatment with penicillin intrathecally and sulfadiazine. The organism was sensitive to 0.24 unit of penicillin per cc. and this concentration was easily exceeded in the spinal fluid by daily administration of 10,000 units.

Meningitis due to N. flava and N. catarrhalis simulated meningococcic meningitis clinically. The former was readily cured by sulfonamides, the latter did not respond.

One unusual meningitis due to Listerella monocytogenes was not helped by sulfadiazine. One patient with syphilitic meningitis did not respond to penicillin.

PROGNOSTIC FACTORS

It became apparent from accumulated experience that meningitis of different etiologic varieties might be divided into mild, moderate, and severe types, and that much less vigorous treatment was necessary to produce good results in the milder categories than in the severe. The time factor also seemed important, although not simply in regard to the duration of illness before therapy was begun.

To this end, the several factors which determine prognosis in meningococcic and pneumococcic meningitis have been analyzed (Table 4). Other types of meningitis might be expected to produce similar data if sufficient cases were available for statistical analysis. Obviously it is impossible to reduce the individual patient to a group of indices, as nothing can replace good clinical judgment. On the other hand, bedside evaluation may be guided successfully by attention to these factors, and hence therapy may be directed more intelligently.

TABLE 4.—*Analysis of Factors Which Determine Prognosis in Meningococcic and Pneumococcic Meningitis*

Sign	Meningococcic Meningitis Per Cent Mortality Present	Meningococcic Meningitis Per Cent Mortality Absent	Pneumococcic Meningitis Per Cent Mortality Present	Pneumococcic Meningitis Per Cent Mortality Absent
Coma	31.4	5.0	81.8	0.0
Hyperpnea	65.2	13.9	92.9	53.8
Age Over 45	58.1	12.6	83.3	43.8
Reduced Spinal Fluid Sugar	22.9	1.9*	66.7	75.0
Bacteremia	21.9	15.8	83.3	14.3
Spinal Fluid Cell Count Less Than 1,000	5.6*	20.7	100.0	61.8
Pneumonia	..	..	88.0	46.2

* Excluding two fulminant cases with minimal meningitis.

In both meningococcic and pneumococcic meningitis, marked interference with consciousness—either coma, stupor or severe delirium—affected the outcome adversely. One hundred and two patients with meningococcic and 33 with pneumococcic infections exhibited severe alterations of consciousness on hospital entry. In epidemic men-

ingitis the mortality of patients with a clear sensorium was less than one-sixth that of those who had sensorial changes. No patient with pneumococcic meningitis who was completely conscious died, as against 81.8 per cent fatality in the comatose group. Conversely, return of consciousness is the best single favorable prognostic sign in any type of meningitis.

Hyperpnea was likewise an evil omen in both types of infection. This peculiar type of respiration, which occurred in our series in 15 patients with meningococcic and in 14 with pneumococcic infections, often approximated that seen in diabetic acidosis, although neither alteration in body chemistry nor increased intracranial pressure was demonstrated as the cause in any of our patients. This hyperpnea must be distinguished from Cheyne-Stokes and Biot's breathing which are often concomitants of increased intracranial pressure and are not of great prognostic significance by themselves. The mortality associated with this sign was 65.2 per cent in meningococcic and 92.9 per cent in pneumococcic infections.

The age of the patient was important in determining the prognosis. Of 31 patients over 45 years of age with epidemic meningitis, 58.1 per cent died, as compared to an overall mortality of 20.3 per cent. Similarly, of 24 patients over 45 years of age with pneumococcic infections, 83.3 per cent expired. None of four patients under one year of age with meningococcic meningitis died. No patient with pneumococcic meningitis fell into this young age group. On the other hand, influenzal meningitis is most lethal under one year of age.[1]

Pneumonia was present in 25 patients with pneumococcic meningitis and of these, 88 per cent died. Patients with other foci such as otitis, mastoiditis, sinusitis and skull fractures did not have a higher mortality than those in whom no focus was demonstrable. Four of our patients with pneumococcic meningitis—three in the sulfonamide treated group, and one in the combined therapy group—recovered from their meningitis only to succumb later to pneumococcic endocarditis. This high incidence affected our mortality figures adversely, especially in the group treated with sulfonamide alone. Pneumonia was a relatively uncommon but unfavorable complication on entry in meningococcic meningitis.

LABORATORY FINDINGS

Bacteremia was of much more diagnostic than prognostic significance in meningococcic meningitis, and probably should be considered an integral part of the clinical picture of almost every case at some stage of its course. Conversely, pneumococcic bacteremia was associated with a mortality of 83.3 per cent, while the death rate in patients with sterile blood cultures was only 14.3 per cent.

Examination of the spinal fluid also may aid materially in determining the prognosis. The mortality rate for patients with epidemic meningitis whose spinal fluids contained less than 1,000 cells per cmm. was low (5.6 per cent) if obvious fulminant examples of the Waterhouse-Friderichsen syndrome, who die before significant infection of the meninges occur, are excluded. On the other hand, six cases of pneumococcic meningitis with a spinal fluid cell count of less than 1,000 per cmm. had a mortality rate of 100 per cent. High cell content of the spinal fluid was no indication of the severity of the infection.

The prognostic significance of the spinal fluid sugar content has been emphasized by others.[1] Spinal fluid sugar analyses were done by the Folin-Wu method whenever possible, but rapid approximate determinations as described by Alexander and associates[1] were of great aid and convenience. Excluding two fulminant cases of meningococcic disease with minimal meningitis, only 1.9 per cent of patients whose spinal fluid sugar was normal died; likewise a rising spinal fluid sugar level usually presaged recovery.

In pneumococcic meningitis the initial sugar level was of no prognostic significance, but again a rising level usually meant that recovery would follow.

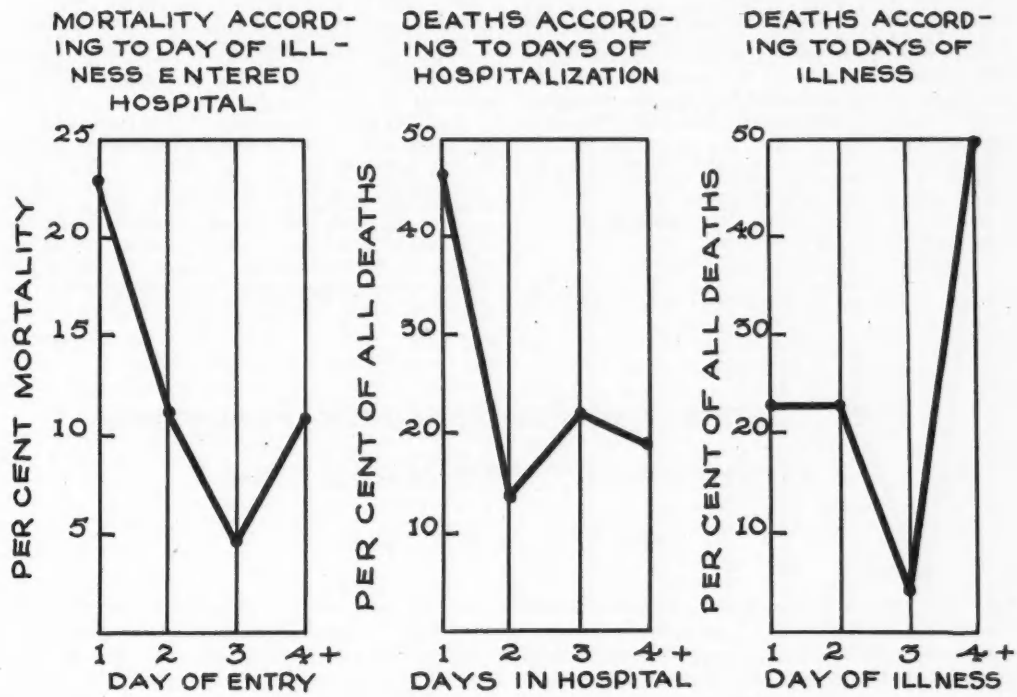
Shock, chronic alcoholism, and coexistent serious diseases affected the outcome adversely. On the other hand, the initial white blood count, the spinal fluid chloride content, the presence of urinary abnormalities including glycosuria, and positive spinal fluid smears or cultures were of little or no value in estimating severity.

In meningococcic meningitis the time factor was important in several ways and could be used as an aid in determining the prognosis and guiding treatment (Table 5). The mortality was highest in those patients who entered the hospital on their first day of illness. These patients, then, may be considered to be those whose infections were due to virulent organisms and were of severe and dramatic onset. The lower mortality of patients entering later in the course of their illness suggests that, if the disease is not severe enough to make early hospital entry necessary, the outlook is good. On the other hand, 50 per cent of deaths occurred on the fourth or later days of illness in those patients from whom a history could be obtained, although almost as high a proportion, 45.6 per cent, died within 48 hours of onset.

On this basis, fatal cases may be divided into two categories: one, in whom the disease is due to an overwhelmingly virulent infection against which therapy is often unavailing and, two, those patients where the infecting organism may be of ordinary virulence, but where irreversible changes, complications, or delayed treatment cause a fatal outcome. The greatest number of deaths on any hospital day occurred on the day of entry—46.9 per cent of all deaths—after which the rate declined rapidly. These patients, of course, died before receiving adequate treatment. If a patient survives the first hospital day, the chances of recovery are excellent. In pneumococcic meningitis, on the other hand, the duration of illness before treatment seemed to have little significant effect on the outcome.

By analyzing all these factors in each individual

TABLE 5.—*Showing Relatively High Mortality Among Patients Hospitalized on First Day of Illness*



patient, the severity of the infection may be estimated and treatment adjusted accordingly.

PLAN OF TREATMENT

Meningococcic Meningitis: Young patients whose disease has been of gradual onset and whose consciousness is intact, especially if the spinal fluid cell count is low and the sugar high, may best be treated with oral sulfadiazine or sulfamerazine.

Other patients, and those who manifest coma, hyperpnea, or shock, or in whom the onset has been severe and abrupt, especially if treatment has been delayed, should be treated by intramuscular and intrathecal penicillin, and, as soon as hydration is satisfactory, by parenteral sulfonamides. Adrenal cortical hormone and plasma may be used to combat shock, although the value of the former is based largely on theoretic grounds. Intrathecal penicillin should be continued daily until the spinal fluid is sterile and the sugar content normal.

Pneumococcic Meningitis: Young patients who are not comatose, and who do not have pneumonia or bacteremia may be treated with either sulfonamides or penicillin alone. Older patients who have one or more of the several unfavorable prognostic signs are probably best treated by combined sulfonamide and penicillin, although the value of such a combination is open to question. Any foci amenable to surgery should be eliminated.

Streptococcic and Staphylococcic Meningitis: Penicillin, administered both intramuscularly and intrathecally, is the treatment of choice. Additional sulfonamides are probably not necessary unless response is delayed. Drainage of foci is important and should be instituted as soon as the infection is controlled.

Hemophilus Influenzae Meningitis: Sulfonamides in large doses for at least two weeks are necessary. Type B rabbit serum should be administered intravenously in infections of this type until the spinal fluid is sterile, the spinal fluid sugar is normal, and the patient's serum will produce capsular swelling of his own infecting organism. Occasional strains may be sensitive to penicillin, so that this should always be investigated.

Coli-Aerogenes Meningitis: Sulfonamide therapy in full dosage is the treatment of choice.

SUMMARY

1. The relative efficacy of sulfonamides, penicillin, and sera, as well as combinations of these agents, is estimated in various forms of meningitis.

2. The effects of various factors on the prognosis of meningitis are analyzed.

3. A plan of treatment for each type of meningitis is promulgated according to these data.

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The Treatment of Pneumococcic Pneumonia With Penicillin and Sulfadiazine*

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WITH present day methods of treatment, the gross fatality rate of pneumococcic pneumonia in adults is 1.5 per cent.[1] Therapy is relatively simple in the majority of cases. However in about 20 per cent of patients there arise special problems in management and treatment which require careful evaluation if the outcome is to be satisfactory.

The therapeutic regimen herein outlined has been developed as a result of the experience with approximately 3,000 patients with pnuemonia over the past four years. The diagnosis of pneumonia was substantiated in every case by indisputable physical findings and a positive roentgenogram.

In this series about 80 per cent of pneumonia was caused by the pneumococcus. (Table 1.) Sputum examinations in each of these cases showed the predominant organism to be the pneumococcus. Specific typing by the Neufeld method was obtainable in 70 per cent of cases.

Even before penicillin was available for treatment the majority of patients with pneumonia presented simple therapeutic problems; they responded easily to usual doses of sulfadiazine and recovered promptly. Pneumococcic pneumonia classified as mild or moderately severe was even then no problem in treatment and had no appreciable fatality rate. However, in 20 per cent of cases the illness was of sufficient severity to warrant special adjuvant therapy in the form of type specific antipneumococcus serum, and in this group the mortality rate was 26.9 per cent (Table 2).

TABLE 1.—*Bacterial Etiology of Pneumonia in 3,075 Consecutive Patients (1942-1946).*

Organism	Number	Per Cent
Pneumococcus	2,379	77.3
Staphylococci } Streptococci {	163	5.3
Virus	110	3.6
Undetermined	427	13.8
	3,079	100.0

TABLE 2.—*Comparative Mortality Rates, According to Severity and Treatment.*

Severity	Therapy	Number Cases	Per Cent Incidence	Per Cent Mortality
Mild and Moderate	Sulfadiazine or Penicillin only	1,269	78.3	0.3
Severe	Penicillin and Sulfadiazine	195	22.4	6.7
	Serum and Sulfadiazine	156	20.9	26.9

With the advent of penicillin, the same majority of patients were no problem in treatment; 78 per cent recovered promptly with simple doses of either sulfadiazine or penicillin, orally or parenterally. However, one out of every five patients was classified as severely or critically ill and received combined sulfadiazine and penicillin therapy (Table 2), with a resultant decrease in mortality from 26.9 to 6.7 per cent.[1]

It is for this latter group of severely ill patients that the skilful evaluation of all factors influencing prognosis, and the meticulous observation of all details in treatment, will be necessary in order to obtain low mortality rates.

Since the advent of chemotherapy, there has been an increasing tendency to discontinue the determination of the bacterial etiology of pneumonia

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by the examination of the sputum and blood culture. This is inadvisable for many reasons.[2]

Probably the simplest and most valuable single procedure is the examination of a stained smear of sputum and the determination of the predominant organism and the approximate number of these organisms present. The prognostic significance of the number of pneumococci per oil immersion field has been demonstrated by Frisch, Price, and Myers,[7] who showed a close relation between the fatality rate and the sputum pneumococci count.

Patients who have only a few pneumococci (under 10 per oil field) have mild pneumonia with the low mortality rate of 0.4 per cent,[2] a low incidence of complications and of bacteremia. This group and those with moderately severe pneumonia (showing 11 to 30 pneumococci per oil field) are easily treated and respond well to simple therapy.

Patients who show many pneumococci in their sputum (31-74 per oil field), and especially those in whom the sputum is loaded with organisms (over 75) are severely ill patients with a very high mortality rate (5 to 15 per cent), and a high incidence of complications. This group requires vigorous therapy with large doses of both penicillin and sulfadiazine.

TABLE 3.—*Comparative Per Cent Mortality by Age and Treatment*[1].

Age	Sulfadiazine with Adjuvant Serum	Sulfadiazine with Adjuvant Penicillin
10-19	0.0	0.0
20-29	2.1	0.0
30-39	2.8	0.5
40-49	5.8	1.9
50-59	14.3	4.1
60-69	12.0	1.2
70 & Over	12.5	10.0
All cases	6.2	1.5

The remarkable effectiveness of combined penicillin and sulfadiazine treatment in all specific types of pneumococcic pneumonia makes routine typing no longer necessary for treatment.[1] The practical importance of typing of pneumococci is further minimized by the fact that the characteristics of each are removed by the uniformity in response to penicillin. However, an occasional patient with an overwhelming pneumonia, with complications such as meningitis, may still require specific antiserum in addition to both penicillin and sulfadiazine.

Probably the most important factor to note as influencing prognosis is age, because of its direct effect on mortality rate and its simplicity in determination. The fact, that regardless of therapy, the mortality from pneumococcic pneumonia is very low in adults under 40, is extremely reassuring in treating patients in this age group (Table 3). With penicillin and sulfadiazine treatment, no adult under the age of 40 with uncomplicated pneumococcic pneumonia should die. Over the age of 40 the fatality rate suddenly rises, and since about 50 per cent of patients with pneumococcic pneumonia are over 40, the factor of age is an extremely important one. The higher incidence of associated diseases in older age groups is an important contributory factor to their high mortality rates.

Frequently a disease occurring concomitantly with pneumonia may become so severe and important a problem that it may become more serious than the pneumonia itself, or may contraindicate certain measures important in the treatment of the pneumonia.

Associated diseases classified as mild usually offer no difficulties of their own in treatment, rarely alter the treatment of the pneumonia, and do not significantly affect the mortality rate (Table 4). Moderately severe concomitant illnesses usually require careful management, often interfere with the routine treatment of pneumonia and result in a higher mortality rate.

Associated diseases classified as severe are always difficult therapeutic problems because two diseases, either one of which alone could kill the patient, are occurring together. Table 4 shows that in this group, combined penicillin and sulfadiazine treatment is very effective, resulting in a decrease in mortality rate from 75 per cent to 18.8 per cent.

In Table 5 are presented in tabular form the practical application of the important prognostic factors in treatment. If none of the severe factors are present (i.e., patient is under 40, sputum count under 30, only a single lobe is involved, etc.) the mortality rate is practically zero with any dosage schedule of either penicillin or sulfadiazine. This is the ideal group to treat with oral penicillin.

Any one of the factors listed in column II (Table 5) tends to increase the mortality rate from 2.5 to 10 per cent, depending upon the factor (average 4 per cent). These patients require full and adequate doses of penicillin preferably, and parenterally administered, or an increased fatality rate will result.

Patients who manifest any single factor listed under column III (Table 5) or multiple factors under column II are usually critically ill—have an

TABLE 4.—*Comparative Mortality by Associated Diseases and Treatment,*

Associated Diseases	Sulfadiazine with Adjuvant Serum: Number of Cases	Sulfadiazine with Adjuvant Serum: Per Cent Mortality	Sulfadiazine with Adjuvant Penicillin: Number of Cases	Sulfadiazine with Adjuvant Penicillin: Per Cent Mortality
Present	142	10.6	193	4.7
Mild	34	5.9	100	1.0
Moderate	43	0.0	77	6.5
Severe	16	75.0	16	18.8
Total (graded)	93	15.1	193	4.7
Not graded	49	2.0	0	0
Not present	606	5.1	679	0.6
Total	748	6.2	872	1.5

average fatality rate of 15 to 20 per cent—and require *combined* penicillin and sulfadiazine therapy for satisfactory outcome.

TABLE 5.—*Indications for Combined Penicillin and Sulfadiazine Therapy.*[2]

Factor	II Severe (More Than Two Factors Below Indicate Combined Therapy)	III Very Severe (Any One Factor Below Is Indication for Combined Therapy)
Age	Over 40	
Sputum count	30 to 75	Over 75 per oil field
Lobes involved	2 or 3	4 or 5
Pulse rate	Over 120	Over 140
Blood Pressure	Systolic, Under 90 / Diastolic, Under 60	Shock or pulmonary edema
Leukocyte count	6,000 to 10,000	Under 6,000
Albuminuria	+++ to ++++	
Associated disease	Moderate	Severe
Complications	Empyema, Lung abscess	Meningitis, Endocarditis
Blood culture	Positive	
Pneumo. Type	I, II, III, IV, VII	

It must be emphasized that no single factor is infallible or can be used to the exclusion of all others. The best evaluation is obtained by applying all the facts available.

This demonstrates the manner in which the severity of the disease is evaluated, which in turn determines how vigorously the patient is to be treated. Now, to develop how the magnitude of dosage to be administered is determined.

Penicillin is the drug of choice in the treatment of pneumococcic pneumonia because it is an extremely effective antipneumococcic agent, and has practically no toxicity in any dosage. Although sulfadiazine is also a very effective drug in the treatment of pneumococcic pneumonia, and prior to the advent of penicillin was the drug of choice, toxic reactions are frequent, occasionally even fatal, and are often of such nature as to require cessation of chemotherapy even though the infection is not yet adequately controlled. In patients with congestive heart failure, renal insufficiency, or conditions tending to produce edema, acidosis or dehydration there often occurs difficulty in maintaining urinary output and preventing crystalluria and urinary obstruction.

It may be stated categorically that penicillin should be given to every patient with pneumococcic pneumonia. Although there is some variation in sensitivity to penicillin among the different strains of pneumococci, they all respond to levels of penicillin usually easily obtained with ordinary therapeutic doses. Table 6 (from Meads[9]) shows that practically all pneumococci are sensitive *in vitro* to levels of 0.05 unit per cubic centimeter, and certainly levels of 0.1 unit will be sufficient for all the usual pneumococcic infections. However, the therapeutic level for severe infections is probably several times the *in vitro* sensitivity levels.

TABLE 6.—*Penicillin Sensitivity of 88 Strains of Pneumococci (From Meads et al*[9]*).*

Number of Strains	10	50	26	2	0
Oxford units per cc.	.008	.016	.031	.063	.125

The administration of penicillin by continuous intravenous drip produces fairly predictable blood levels of penicillin.[10] Giving 60,000 units daily in this manner maintains blood levels about 0.05 unit per cubic centimeter (Table 7) which is sufficient dosage for the majority of strains of pneumococci (Table 6). By intramuscular injection, about twice the daily dosage is required to obtain the same blood levels, so about 120,000 units per day or 15,000 units every three hours, should be sufficient dosage for the majority of pneumonias, and certainly for the mild or moderately severe pneumonia. For very severe pneumonia, blood concentrations several times the *in vitro* sensitivity level are required, which means that blood levels of 0.1 or 0.2 unit or even higher must be obtained. This will require doses of 250,000 units daily by continuous intravenous drip, or 40,000 to 50,000 units every three hours intramuscularly. The administration of penicillin by continuous drip is reserved now for only the severest of pneumonia, where the maximum blood levels obtainable are desired.

TABLE 7.—*Approximate Plasma Concentration of Penicillin Administered by Continuous Intravenous Drip (From Rantz & Kirby*[10]*).*

Units of Penicillin		(Units Per cc.)
Per Hour	Total Per Day	Plasma Concentration
2,500	60,000	0.05
5,000	120,000	0.10
10,000	240,000	0.20
20,000	480,000	0.40

Studies have confirmed the reliability of treating mild and moderately severe pneumonia with orally administered penicillin.[3] The clinical results obtained in such instances are in no way different from those observed in patients treated with parenteral penicillin. Adequate absorption of orally administered penicillin is obtained if it is combined with agents which prevent it from being inactivated by gastric acid. Calcium carbonate and sodium citrate appear to be the most effective of the antacid group in aiding penicillin absorption.[11] It has been demonstrated[3] that 100,000 units of calcium penicillin combined with two grams of calcium carbonate administered orally every two hours maintains blood levels between 0.04 and 0.08 unit, which is adequate. Subsequent studies have shown that the frequency of doses can be decreased to every three hours and adequate blood levels are maintained.

In summary, the specific treatment of uncomplicated pneumococcic pneumonia in adults may be briefly outlined as follows:

I. MILD OR MODERATELY SEVERE PNEUMONIA

1. Preferred treatment:

Penicillin tablets: 200,000 units orally stat, then 100,000 units every three hours. Doses at or about meal times to be given preferably one-half hour before meals,

a. Omit doses between midnight and 6:00 a.m.

b. Discontinue after temperature normal three days. (To avoid relapses, penicillin must be continued somewhat longer than is ordinarily considered sufficient for sulfadiazine.[8])

2. Alternate treatment:

Penicillin solution: 15,000 units intramuscularly every three hours.

a. and b., same as with penicillin tablets.

3. Satisfactory, but not recommended:

Sulfadiazine: Grams 5 orally initially, then grams 2 every six hours.[5]

a. Soda: grams 5 q.i.d. (15 to 20 grams daily.[8])

b. Maintain urinary output over 1,500 cubic centimeters daily with pH 7.5 to 8.0. Blood counts every two to three days.

c. Discontinue after temperature normal two days.

II. Severe Pneumonia

(Combined "Low-Dose" Routine.)

1. *Penicillin solution:* 25,000 units intramuscularly every three hours.

2. *Sulfadiazine:* Orally grams 5 initially, then grams 2 every six hours.

a. Precautions against sulfadiazine toxicity, same as for I, 3a and 3b above.

Discontinue sulfadiazine after temperature normal two days. Discontinue penicillin after temperature normal three days. Non-specific therapy (oxygen, etc., as indicated). (Routine admission blood count, blood culture, chest film, and sputum pneumococci count for all cases.)

III. Very Severe (Overwhelming) Pneumonia

(Combined "High-Dose" Routine.)

1. *Penicillin solution:* 40,000 units intramuscularly every three hours, or 10,000 units per hour by continuous intravenous drip.

2. *Sodium sulfadiazine:* Grams 5 in 500 cubic centimeters 1/6 M sodium lactate solution.

3. *Sulfadiazine:* Grams 4 orally every six hours. (High doses of sulfadiazine result in a great decrease in mortality rate without any increase in toxicity.[6])

a. Adequate alkalization ($NaHCO_3$, $KHCO_3$, Na lactate) to maintain urinary pH 7.5.

b. Maintain urinary output over 1,500 cubic centimeters.

c. Other precautions against sulfadiazine toxicity.

Determine penicillin and sulfadiazine susceptibility of organisms. (Other routine laboratory work should be obtained before specific therapy is instituted.) Determine penicillin and sulfadiazine blood levels, and alter dose schedule accordingly. After satisfactory response, continue as for II.

The innumerable details of the treatment of complications and associated diseases are a special problem in themselves.

SUMMARY

Penicillin is the drug of choice in the treatment of pneumococcic pneumonia because of its effectiveness and lack of toxicity. In mild and moderately severe pneumonia, orally administered penicillin is preferred because of its ease of administration and good clinical results. For severe pneumococcic pneumonia, combined parenteral penicillin and sulfadiazine is the most effective therapy.

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Antibiotics in the Treatment of Hemolytic Streptococcus Sore Throat*

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THE treatment of hemolytic streptococcus sore throat with a rash (scarlet fever) and without a rash has been unsatisfactory. Although the several sulfonamides have been widely used in the management of this disease, convincing evidence is not available which demonstrates that their administration is associated with a decrease in the length or severity of the illness, a mitigation of the symptoms, or a more rapid resolution of the lesions in the throat. It is clear that sulfonamide therapy during the acute illness will not prevent the development of rheumatic fever and the other serious late nonsuppurative complications of hemolytic streptococcal disease.

Because the results of sulfonamide therapy were disappointing and because of the importance of hemolytic streptococcal respiratory disease, great interest was aroused by the development of penicillin as an available chemotherapeutic agent and by the demonstration that Group A hemolytic streptococci were extremely susceptible to its action. Several clinical studies[1,2,4] were undertaken for the purpose of determining its efficacy in the treatment of hemolytic streptococcus sore throat, the results of which may be summarized.

The administration of 100,000 to 200,000 units of penicillin per day by the intermittent, intramuscular route is followed by the rapid disappearance of hemolytic streptococci from the throat and nose of infected individuals. Coincidentally there is often a moderate amelioration of symptoms and a reduction in the temperature. It is disappointing to learn that the average severity of disease, and the duration of fever and abnormal physical signs in the throat are not materially reduced in penicillin treated patients when data derived from the study of such cases is compared with those obtained in untreated groups.[3] Furthermore, if penicillin therapy is not continued for at least five days, bacteriological and, in many cases, clinical relapse will follow its withdrawal. The disease will be more prolonged under these latter circumstances than in untreated individuals.

Sulfonamides have been administered for ten or more days after a short course of penicillin in certain studies in the hope that such a clinically useful regime might avoid the hazards of relapse. This expectation was not realized; recrudescence of disease in patients treated in this manner was simply delayed until discontinuance of the sulfonamide.

It is probable that adequate early treatment of hemolytic streptococcal sore throat with penicillin will prevent the development of suppurative complications such as otitis media, peritonsillar abscess and sinusitis. The evidence thus far accumulated indicates that late nonsuppurative complications occur as frequently in penicillin treated cases as in untreated persons.

Penicillin therapy of hemolytic streptococcal sore throat in adults should be reserved for severely ill cases. Its more frequent use in children may be desirable because of the common occurrence of suppurative complications. If this antibiotic is to be used, it should be administered in a dosage of 100,000 to 200,000 units per day by the intermittent intramuscular route; 100,000 units six times per day on an empty stomach by the oral route; or 300,000 units injected once daily intramuscularly if penicillin-oil-beeswax is to be used. In every case, therapy should be continued for a minimum of five days.

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Nitrous Oxide and Oxygen Anesthesia With Curare Relaxation*

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NITROUS oxide anesthesia has been the subject of bitter controversy ever since its first public demonstration by Horace Wells in 1844. Not until Andrews showed that the admixture of oxygen with nitrous oxide increased its safety was it considered sufficiently flexible for use in general surgery. Profound differences of opinion have been very much in evidence among anesthetists, physiologists and pharmacologists regarding the status of nitrous oxide anesthesia. The extremes of viewpoint range from those who believe that nitrous oxide is sufficiently potent to afford adequate anesthesia for all kinds of abdominal operations to those who feel that nitrous oxide is incapable of producing anesthesia independent of oxygen lack. At present the consensus appears to favor the contention that nitrous oxide with oxygen in atmospheric proportions will produce light surgical anesthesia, but only slight muscular relaxation.

The practice of producing greater depth of narcosis by restriction of oxygen in nitrous oxide-oxygen mixtures has been properly discredited but frequently resorted to in order to avoid the addition of ether. Many recently trained anesthetists have had little experience with nitrous oxide anesthesia. The popularity of cyclopropane anesthesia, wherein any degree of narcosis might be maintained without danger of oxygen lack, has been a strong reason for the failure to use nitrous oxide to its fullest extent.

One has only to review briefly the physical and physiological advantages of nitrous oxide and oxygen anesthesia to understand the desirability of a re-investigation of its present status in the light of recent advances in the clinical use of curare.

Nitrous oxide and oxygen provide us with a general anesthetic which is neither inflammable nor explosive and which is relatively non-toxic. Its inability to produce adequate muscular relaxation in the majority of abdominal operations is well recognized. Pre-anesthetic medication with narcotic drugs increases, markedly, the field of usefulness of nitrous oxide and this field may be broadened further by the use of nerve blocks with solutions of local anesthetics.

The introduction of clinically adequate curare into anesthesia offered the possibility of the greatest advance in gas anesthesia since Andrews suggested the combination of oxygen with nitrous oxide.

When Griffith first decided to use curare to secure muscular relaxation during light surgical anesthesia, it was only natural for him to select cyclopropane, of which he is a leading exponent, for the trial. Nevertheless, curare appeared to the authors of this paper to offer a means whereby muscular relaxation or even flaccidity might be obtained during the course of anesthesia with nitrous oxide. Decision to study it was motivated by a desire to extend the physiological advantages of nitrous oxide anesthesia, rather than a wish to veer away from cyclopropane or ether solely because of their inflammable nature. Observations herein are based on experience with the use of nitrous oxide anesthesia with curare relaxation in a wide variety of cases, 160 in number, during the last two years.

ADEQUATE PAIN RELIEF AND REFLEX OBTUNDATION

Very early in the study the observation was made that the attainment of adequate muscular relaxation might not be the only obstacle to be overcome in this effort to widen the scope of nitrous oxide anesthesia. Even when curare was administered in doses sufficiently large to provide good muscular relaxation, there was evidence of insufficient pain relief during the period of manipulation of the abdominal viscera. The patient will usually respond to such stimulation by contracting, however, feebly, the musculature which the curare has not completely paralyzed, such as the muscles of the face. A grimace is observed and the pulse and blood pressure will usually rise simultaneously. The intravenous administration of morphine will cause the grimace to disappear and the blood pressure and pulse may assume their pre-manipulative level.

The well-known respiratory embarrassment consequent upon the intravenous administration of morphine led us to try Demerol. Clinically, Demerol given intravenously in doses of 50 to 100 mg. will fortify the pain-relieving qualities of nitrous oxide and oxygen with less respiratory depression than that observed following equivalent doses of morphine. Not only will the degree of respiratory depression be less profound, but it will be of much shorter duration, ranging in the neighborhood of one-half hour in the average case. Curare relaxation should, in our opinion, never be considered a substitute for adequate pain relief, even though the patient may, by reason of certain hypnotic drug action, have a complete amnesia for the horrible experience. The administration of curare should be reserved until complete freedom from the effects of painful stimuli can be guaranteed. This having been done, curare may then be administered in amounts sufficient to obtain the required relaxation of the skeletal musculature.

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EFFECTS OF NARCOSIS AND CURARIZATION ON VENTILATION

Regardless of the drugs used for narcosis, anesthesia, or muscular relaxation, the primary concern should be the maintenance of optimum pulmonary ventilation. All anesthetics and narcotics employed to produce general depression of the central nervous system are respiratory depressants. The narcotic drugs such as morphine afford good pain relief with only moderate respiratory depression, in contrast to the hypnotic drugs, including the barbiturates of all classes, which produce marked respiratory depression with only slight pain relieving qualities. The so-called intravenous anesthetics, pentothal and evipal, fall into this category and might better be regarded as "super-hypnotics" than anesthetics.

Nitrous oxide and oxygen, plus intravenous Demerol, plus curarization, afford good anesthesia and excellent muscular relaxation. On the other hand, one must be prepared to deal with the additive depressant action of each of these drugs on respiration.

When the patient has been given enough of the aforementioned drugs to produce good surgical anesthesia, it has been our practice to supplement the patient's feeble respiratory efforts by rhythmically inflating his lungs. This may most efficiently be accomplished by using the "to and fro" carbon dioxide absorption system and exerting gentle intermittent pressure on the breathing bag. The airway should be perfectly free. To insure this, endotracheal intubation is highly desirable. This has been our practice in most intra-abdominal procedures. Under circumstances wherein the patient has been intubated, one may be assured that the compression of the breathing bag will result solely in the inflation of his lungs. In some cases, where the control of ventilation was attempted without endotracheal intubation, there was a marked distention of the stomach and intestines simultaneous with the inflation of the lungs. Indeed, this has been demonstrated in a cinema intended to illustrate the use of curare in anesthesia! In some instances where the anesthetist fortifies the patient's spontaneous respiratory movements to insure adequate ventilation, it will be observed that the respiration has become completely under his control. Adequate ventilation may be guaranteed by the rhythmic, intermittent inflation of the lungs, allowing expiration to proceed passively against only atmospheric pressure. When spontaneous respiratory movements of sufficient amplitude have returned, the mechanical assistance may be discontinued.

Under-ventilation will be noticed much more quickly during nitrous oxide anesthesia than when agents such as cyclopropane or ether, which carry a much higher complement of oxygen, are employed. It has been our practice to combine nitrous oxide with 20 per cent or more of oxygen checked by actual gas analysis. Frequent gas samples were taken for analysis during the course of many operations. The residents are instructed to feel free to make these determinations at any time, in any case. This procedure tends to make all the anesthetists avoid oxygen deprivation.

The respiratory depression consequent upon the administration of curare is different in character from that which is produced by increasing the depth of narcosis with the various general anesthetics. Curare and the potent anesthetics, such as ether, both produce inactivity of thoracic respiratory movements before diaphragmatic paralysis, but here the similarity ceases. When ether anesthesia is pushed to the point where the intercostal musculature becomes paralyzed, the diaphragmatic movements appear to be very little affected. This phenomena offers a marked contrast to the combined paralysis of the intercostal musculature and paresis of the diaphragm observed following the administration of curare. Spontaneous respiratory movements which result in little more than the displacement of the dead space air back and forth are not satisfactory for the purpose of ventilation.

When the administration of curare is superimposed on anesthesia with cyclopropane, combined with very high proportions of oxygen, cyanosis will naturally be more slow in appearing than during nitrous oxide anesthesia when atmospheric proportions of oxygen are employed. Regardless of the degree of oxygenation of the blood, its carbon dioxide tension may be dangerously elevated by depressed respiration. When carbon dioxide is permitted to accumulate in the patient who has received curare, the usual increased blood pressure response may not occur until the curare action has partially or totally worn off. It would appear that the reason for this has to do with the decreased peripheral resistance of the vascular bed consequent upon the general relaxation of the skeletal musculature. The pulse rate increase which follows an elevated carbon dioxide tension in the blood will be observed in the under-ventilated patient who has received curare. When the effect of curare has worn off, under-ventilation will cause the blood pressure to rise. It is important to note at this point that insufficient pain relief in the patient who is adequately ventilated will cause the blood pressure to rise when the curare action has become dissipated. The differentiation is important and is a matter for the physician familiar with respiratory physiology to decide. The treatment for the former is supplemental ventilation; for the latter, supplemental anesthesia. Perhaps by reason of our concern with the problems of ventilation during the course of anesthesia for intrathoracic operations, we have not experienced any untoward effects of over-ventilation, although conceivably this might occur. Here again, emphasis must be placed on the qualifications of the individual conducting the anesthesia and the ventilation rather than the person administering the curare. We believe that the former should never be delegated to anyone except a properly qualified physician anesthetist, while the latter may be performed by anybody who is able to insert a needle into a vein. These matters are stressed because of the all too frequent experience of witnessing the reverse. This, too, was recently demonstrated in a cinema intended to show the technique of controlling ventilation during cyclo-

propane anesthesia in a patient who had been given curare.

PROPER TIME OF CURARE ADMINISTRATION

When curare is employed as a means of obtaining satisfactory muscular relaxation during nitrous oxide anesthesia, it should only be given after adequate pain relief has been assured. After nitrous oxide anesthesia has been induced by the carbon dioxide absorption technique, Demerol, given intravenously and slowly enough so that respiration is not too greatly depressed (usually 50 to 100 mg.), is injected over a period of three to four minutes. Adequate pain relief thus having been achieved, curare in the amount of 80 or 100 mg. may be administered intravenously to insure sufficient relaxation for endotracheal intubation. Subsequent doses of curare may then be given as needed to secure the necessary muscular relaxation. The dose required for the subsequent injections has ranged betwen 40 and 60 mg. of curare. During the course of operations lasting four hours or longer, it will usually be necessary to give additional doses of Demerol. We usually administer 25 to 50 mg. intravenously for this purpose. The largest total amount of curare which we have employed in one case was 260 mg. for a bowel resection lasting six and a half hours. The largest amount of Demerol was 225 mg. during a gastric resection lasting four hours.

REVERSAL OF ANESTHETIC, NARCOTIC AND CURARE EFFECTS

The anesthetist should try to conduct every anesthetic in such a manner as to provide the surgeon with the approximation of ideal operating conditions and still guard against any action which will delay the return of the patient's reflexes upon completion of the operation. The reversal of the effects of nitrous oxide is almost immediate. Recovery from the respiratory depressant action of intravenous Demerol takes approximately one-half hour, while the return of the cough reflex may require an additional hour or an hour and a half. The hypnotic action of Demerol is of short duration and patients may readily be awakened 15 to 20 minutes after the intravenous administration of 50 mg. of the drug.

Curare is effective for approximately one-half hour after its intravenous injection. The length of time during which it is effective clinically appears to be affected very little by the size of the dose when it is administered in the amounts which we have employed for obtaining muscular relaxation during nitrous oxide anesthesia. An initial 100 mg. dose appears to last no longer than an 80 mg. dose, although the result of the former may be muscular flaccidity and of the latter muscular relaxation.

CUMULATIVE EFFECTS OF DEMEROL AND CURARE

There is a certain amount of cumulative effect after the administration of repeated doses of Demerol so that the duration of action of the subsequent doses becomes progressively longer.

Curare, also, shows a cumulative action and when large amounts of the drug are required, as in the case of prolonged operations, a sensation of muscular weakness may persist for some hours after the termination of anesthesia.

SUMMARY

1. A method of rendering nitrous oxide anesthesia more flexible by the use of curare for obtaining muscular relaxation has been outlined based on experience in 160 clinical cases.

2. The importance of first securing adequate pain relief before the administration of curare has been stressed. The intravenous injection of Demerol to fortify the anesthetic properties of nitrous oxide has been suggested.

3. The problems of altered respiratory physiology consequent upon the employment of the nitrous oxide-Demerol-curare combination have been discussed.

4. Satisfactory anesthesia for major abdominal operations may be provided by nitrous oxide and oxygen when the skeletal musculature has been relaxed with curare.

5. The toxicity of nitrous oxide and curare are low and the safety of the method depends on the ability of the anesthetist to apply his physiological knowledge to a clinical procedure.

Guest Speakers, C.M.A. 76th Annual Session
Los Angeles, April 30—May 3, 1947

A. W. Oughterson, M.D., *Medical Director*, American Cancer Society, New York City	"Planning the Attack on Cancer" "The Diagnostic Problem in Gastro-Intestinal Cancer"
Hobart A. Reimann, M.D., *Professor of Medicine*, Jefferson Medical College, Philadelphia	"Virus Pulmonary Diseases," "Periodic Diseases" "What's New in Infectious Diseases"
James T. Priestley, *Mayo Clinic*, Rochester, Minnesota	"The Surgical and Physiological Aspects of the Treatment of Duodenal Ulcer"
Albert Snell, M.D., *Professor of Medicine*, Mayo Foundation, Rochester, Minnesota	"The Management of Infectious Hepatitis" "What's New in Gastroenterology"

Poison Oak— New Antigens and Their Effect On Sensitized Guinea Pigs

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DURING the past five years at the Hooper Foundation for Medical Research many poison oak extracts have been prepared for experimental use, using four different solvents. The solids content of each was determined, as well as the quantities of the so-called active principle (the vesicant oleoresin known as lobinol, expressed in Dermatitant Units). They varied greatly. (Table 1.)

TABLE 1

200 grams of fresh poison oak leaves and stems were macerated for one month in 1000 cc. each of four solvents. Filtered. Solids weighed. Lobinal content estimated.

Extract No. 1 (Petroleum Ether)	
Extract 1 L	0.1 cc. contained 5,000 Dermatitant Units of Lobinol.
Extract 1 S	100 cc. contained .170 gram of solids.
Extract No. 2 (Ethyl Ether)	
Extract 2 L	0.1 cc. contained 80,000 Dermatitant Units of Lobinol.
Extract 2 S	100 cc. contained .290 gram of solids.
Extract No. 3 (Ethyl Alcohol)	
Extract 3 L	0.1 cc. contained 20,000 Dermatitant Units of Lobinol.
Extract 3 S	100 cc. contained .725 gram of solids.
Extract No. 4 (Acetone)	
Extract 4 L	0.1 cc. contained 40,000 Dermatitant Units of Lobinol.
Extract 4 S	100 cc. contained 1.000 gram of solids.

Two groups of antigens were prepared from these extracts. One group designated as the "LA" group was prepared on the basis of lobinol content. That is, each of the four extracts was adjusted so that 1 cc. contained 10,000 Dermatitant Units of lobinol. (Table 2.) The other group, designated as the "SA" group, was prepared on the basis of solids content. That is, each extract was adjusted so that it contained 0.1 per cent of solids. (Table 3.)

The antigens were prepared by allowing the extracts to evaporate in a 37 degrees centigrade incubator and redissolving the residue in an inert vehicle (e.g., in peanut oil in the case of the petroleum ether and ethyl ether extracts, and in propylene glycol in the case of the ethyl alcohol and acetone extracts).

Sensitized guinea pigs were treated both intramuscularly and by mouth with these eight extracts according to the method described in a previous paper,[6] excepting that a 5,000 Dermatitant Unit stripe test was adopted instead of the 1,000 unit previously. This increased strength in the testing dose was found to be more exacting than the weaker one because it required a higher degree of immunity to influence it, and for that reason was considered a more accurate gauge of measurement.

White guinea pigs weighing approximately 400 grams each were epilated by plucking the hair and then striped daily with a 5,000 Dermatitant Unit poison oak extract until they became sensitized.[7] The reactions were recorded as one, two, three or four plus on the basis of the intensity of the erythema 48 hours after the stripe test was applied, plus the length of time it took for the crust resulting therefrom to separate. The more intense the reaction, the thicker the crust and the longer it took to separate. Only those pigs developing a 4 plus sensitivity were selected for these experiments.

EXPERIMENT I

Sixty-four sensitized pigs were diveded into two groups of 32. Three pigs from each group received 1 cc. of each of the eight extracts intramuscularly

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This paper is No. III of a series. (See references 6 and 7.)

TABLE 2.—*LA Group: The Four Extracts Adjusted, So That Each Contained 10,000 Dermatitant Units of Lobinol Per 1 cc.*

Medication	By Mouth 1 cc. Daily for 12 Doses — Stripe Test: Before Treatment	By Mouth 1 cc. Daily for 12 Doses — Stripe Test: After Treatment	By Intramuscular Injection 1 cc. Every 3rd Day for 6 Doses — Stripe Test: Before Treatment	By Intramuscular Injection 1 cc. Every 3rd Day for 6 Doses — Stripe Test: After Treatment
Extract No. 1 LA (Petroleum Ether) 1 cc. contained 10,000 Dermatitant Units of Lobinol and .340 mg. of solids.	4+	3+	4+	3+
Extract No. 2 LA (Ethyl Ether) 1 cc. contained 10,000 Dermatitant Units of Lobinol and .036 mg. of solids.	4+	3+	4+	3+
Extract No. 3 LA (Ethyl Alcohol) 1 cc. contained 10,000 Dermatitant Units of Lobinol and .362 mg. of solids.	4+	3+	4+	2+
Extract No. 4 LA (Acetone) 1 cc. contained 10,000 Dermatitant Units of Lobinol and .250 mg. of solids.	4+	3+	4+	2+

TABLE 3.—*SA Group: The Four Extracts Adjusted So That Each Contained .1% of Solids.*

Medication	By Mouth 1 cc. Daily for 12 Doses — Stripe Test: Before Treatment	By Mouth 1 cc. Daily for 12 Doses — Stripe Test: After Treatment	By Intramuscular Injection 1 cc. Every 3rd Day for 6 Doses — Stripe Test: Before Treatment	By Intramuscular Injection 1 cc. Every 3rd Day for 6 Doses — Stripe Test: After Treatment
Extract No. 1 SA (Petroleum Ether) 1 cc. contained .001 gram of solids and 29,500 Dermatitant Units of Lobinol.	4+	2+	4+	3+
Extract No. 2 SA (Ethyl Ether) 1 cc. contained .001 gram of solids and 276,000 Dermatitant Units of Lobinol.	4+	1+	4+	3+
Extract No. 3 SA (Ethyl Alcohol) 1 cc. contained .001 gram of solids and 27,600 Dermatitant Units of Lobinol.	4+	2+	4+	1+
Extract No. 4 SA (Acetone) 1 cc. contained .001 gram of solids and 40,000 Dermatitant Units of Lobinol.	4+	2+	4+	1+

for six doses at three- to four-day intervals and three received 1 cc. of each of the eight extracts by mouth either daily or every other day for 12 doses. After the treatment was completed they were striped tested again at ten-day intervals for four testings (40 days). All of the pigs developed some protection regardless of which extract was used or by which route it was given. However, there was a marked difference in the degree of protection afforded by one extract as compared to another. This difference seemed to depend on the route in which it was administered on the one hand and on the content of solids or lobinol on the other. The immunity was at its height on the 30th day stripe reading and remained unchanged on the 40th day reading. Eight sensitized pigs in each group (16 in all) were used as controls. They were not given any therapy, but were stripe tested each time the treated pigs were tested. These pigs remained sensitive throughout the experiment.

LA GROUP EXTRACTS

Results with the four LA Group extracts by both methods of administration were:

By Mouth: These four extracts produced a slight but equal and uniform amount of protection. The stripe readings were reduced from a 4 plus to a 3 plus reaction for this group.

By Intramuscular Injection: The same four extracts produced varying degrees of protection. Extracts 3 LA (Ethyl Alcohol) and 4 LA (Acetone) were the most efficient with them, the stripe test readings were reduced from 4 plus to 2 plus reactions. With the other two extracts, 1 LA (Petroleum Ether) and 2 LA (Ethyl Ether), the improvement was from 4 plus to 3 plus.

SA GROUP EXTRACTS

Results with the SA Group extracts were:

By Mouth: These four extracts produced varying degrees of protection. Extract 2 SA (Ethyl Ether) was the most efficient. With it, the stripe test reading was reduced from 4 plus to 1 plus, and with the other three the improvement was from 4 plus to 2 plus.

By Intramuscular Injection: The same four extracts also produced varying degrees of protection. Extract 3 SA (Alcohol) and 4 SA (Acetone) were the most efficient, reducing the stripe test readings from 4 plus to 1 plus reactions, while with the other two extracts, 1 SA (Petroleum Ether) and 2 SA (Ethyl Ether), the improvement was from 4 plus to 3 plus.

From the foregoing experiments it appeared that the plant constituent responsible for producing the most immunity in the guinea pig when the extracts were given by mouth was different from that which caused the greatest improvement when administered by intramuscular injection.

The most protection in the "by mouth" treated groups was observed with those extracts containing the greater amounts of lobinol. For instance, Extract 2 SA (Ethyl Ether) containing 276,000 Dermatitant Units, was by far the most efficient. Extract 1 SA (Petroleum Ether) and 3 SA (Ethyl Alcohol) and 4 SA (Acetone) containing 29,500, 27,600 and 40,000 Dermatitant Units respectively, were next, while the other four, each containing 10,000 units, were the least effective. In the intramuscularly treated groups, however, the extracts containing the greater amounts of polar (water soluble) solids produced the most protection. Extracts 3 SA (Alcohol) and 4 SA (Acetone), each containing .001 gm. of solids, were the most efficient while Extracts 3 LA (Alcohol) and 4 LA (Acetone), containing .362 mg. and .250 mg. of solids respectively, were next and the other four extracts (two made with a non-polar solvent 1 LA and 1 SA, and two with a low-polar solvent 2 LA and 2 SA) were the least effective.

In view of these findings it was decided to run similar animal tests with fractions of one of the extracts, namely, No. 3 Extract (Ethyl Alcohol). This extract contained considerable quantities of the polar solids as well as the oleoresin and waxes. The fractions were obtained in the following manner:

Method A: One thousand cc. of Extract No. 3 (Ethyl Alcohol) was diluted with 500 cc. of water. A precipitate occurred which was removed by fil-

tration. This precipitate was soluble in 95 per cent alcohol and insoluble in 62 per cent alcohol and was labeled Fraction 3A. A portion of this filtrate was dried under vacuum and labeled Fraction 3 BC. Another portion of the filtrate was further diluted with water so that the alcoholic content was reduced to 12 per cent. Another precipitate resulted. This was removed by filtration. The precipitate was soluble in 62 per cent alcohol and insoluble in 12 per cent alcohol. It was labeled Fraction 3B. The filtrate, consisting of the 12 per cent alcohol soluble solids only, was labeled Fraction 3C.

Antigens were made from these four fractions by dissolving the precipitates and/or residues in inert vehicles each containing 0.1 per cent of solids. Fraction 3A was the only one which contained enough lobinol to elicit a response when stripe tested on a sensitized guinea pig's skin.

EXPERIMENT II

Thirty-two sensitized guinea pigs were divided into two groups of 16. Three pigs from each group received 1 cc. of each of the four antigens intramuscularly for six doses at three- to four-day intervals, and three received 1 cc. of each of the four antigens by mouth either daily or every other day for 12 doses. After the treatment was completed the pigs were stripe tested again at ten-day intervals for four testings (40 days). The immunity was at its height on the 30th day stripe reading and remained unchanged on the 40th day reading. Four sensitized pigs in each group (eight in all) were used as controls. They were not given any therapy but were stripe tested each time the treated pigs were tested. These pigs remained sensitive throughout the experiment.

Here, again, all of the pigs developed some protection regardless of which antigen was used or by which route it was administered. (Table 4.)

By Mouth: Antigen 3A (the only one containing measurable quantities of lobinol) was the most efficient. The stripe test was reduced from a 4 plus to a 1 plus reading in all three of the pigs. With the other three antigens (3 BC, 3B and 3C) the reduction was from a 4 plus to a 3 plus.

By Intramuscular Injection: Antigen 3 BC and 3C (the two containing the greater percentage of polar solids) were the most efficient. The stripe test in all of the pigs receiving both of these antigens was reduced from 4 plus to 1 plus. With Antigen 3B the improvement was slightly less, the reduction being from 4 plus to 2 plus, while with Antigen 3A, the improvement was noticeably less —from 4 plus to 3 plus.

These latter experiments confirmed previous observations; namely, that the poison oak extracts containing the larger quantities of lobinol were more efficient as immunity builders when given by mouth, and less efficient when administered by the intramuscular route, while the poison oak extracts containing the larger quantities of polar (water soluble) solids, but very little of the lobinol or waxes, were good immunity builders when administered intramuscularly, and less efficient when given orally.

Besides Method "A", already described, several other methods were employed for separating these various fractions. Some produced more efficient and others less efficient antigens. On the whole, however, the results obtained from their administration to sensitized guinea pigs were similar to those observed and recorded with the fractions obtained by Method "A".

In describing some of the other methods used for this purpose, the author has designated as Antigen No. 95 all of those in which the vesicant (the dermatitis producing fraction) was the outstanding constituent; as Antigen No. 62 all of those which contained most of the plant constituents, excepting the vesicant; and as Antigen No. 12 those containing the water soluble fractions only.

Other methods for preparing Antigen No. 95 were:

Method "B": Direct extraction of the fresh leaves, stems, or roots with fat solvents.

Method "C": Secondary extracting, with a fat solvent, of (1) the residue remaining after volitilizing under vacuum, an extract made with a polar solvent, such as alcohol; or of (2) the solution of the plant extract itself, as hereinafter described. (No. 62C.)

Method "D": Precipitating the vesicant from a solution of plant extracts, with one of the heavy metals, such as lead, aluminum, etc., and then purifying the precipitates.

TABLE 4.—*Extract No. 3 (Ethyl Alcohol) Fractionated Into Four Antigens.*

	By Mouth 1 cc. Daily for 12 Doses Stripe Test		By Intramuscular Injection 1 cc. Every 3rd Day for 6 Doses Stripe Test	
Medication	Before Treatment	After Treatment	Before Treatment	After Treatment
Antigen No. 3A Soluble in 95% alcohol. Insoluble in 62% alcohol. 1 cc. contained .001 gram of solids and 60,000 Dermatitant Units of Lobinol.	4+	1+	4+	3+
Antigen No. 3 BC Soluble in 62% alcohol. 1 cc. contained .001 gram of solids.	4+	3+	4+	1+
Antigen No. 3B Soluble in 62% alcohol. Insoluble in 12% alcohol. 1 cc. contained .001 gram of solids.	4+	3+	4+	2+
Antigen No. 3C Soluble in 12% alcohol. 1 cc. contained .001 gram of solids.	4+	3+	4+	1+

Other methods for preparing Antigen No. 62:

Method "B": Extract the fresh leaves and stems with a fat solvent, in order to remove most of the vesicant, dry the leaves and stems and then make a second extraction, this time with a water soluble solvent. This latter extract is evaporated under vacuum and the residue dissolved in propylene glycol.

Method "C": Mix an equal amount of an extract made with a water soluble solvent, such as ethyl alcohol, with a fat solvent, e.g., petroleum ether. Place in a separatory funnel, shake thoroughly and add three volumes of water for each volume of ethyl alcohol present. Shake again. After the layers separate, the upper petroleum ether layer will be found to contain most of the vesicant. The lower layer (alcohol-water), which contains most of the plant constituents excepting the vesicant, is then removed and dried under vacuum and the residue dissolved in propylene glycol.

Method "D": Dry and store the fresh leaves and stems in an incubator at 56°C. for three months. The vesicant evidently undergoes a chemical change under this treatment during this time, and extracts made with this material, using any of the various solvents, produced no reaction when applied to sensitized guinea pig skins. (The same change occurred with leaves and stems stored at room temperatures for much longer periods of time—two years in one instance.)

Other methods for preparing Antigen No. 12:

Method "B": Treat the fresh leaves and stems with boiling water (as in making infusions). Filter several times with talcum in order to remove all traces of the suspended vesicant.

Method "C": Extract the leaves and stems with a 12 per cent water soluble solvent (alcohol, acetone, etc.).

Method "D": Evaporate extracts made with water soluble solvents, under vacuum, and then extract the residue with water or with 12 per cent. alcohol.

The No. 12 antigens made according to Methods "B" and "C" were potent if given subcutaneonsly within the first few hours or days, but they darkened on standing and as this occurred they also lost their potency. Attempts to prevent this change by adding antioxidants were unsuccessful.

Inasmuch as the intramuscular injection of a No. 12 antigen proved to be of value in reducing the sensitivity to poison oak in guinea pigs, the following chemical analyses were made of this fraction (100 cc. contained 150 mg. of solids):

1. *Total Nitrogen: 0.011 mg./cc.* (Mean of six determinations.) Determined by the microkjeldalh method.

Protein Nitrogen: Too little to detect. (Mean of three determinations.) Determined by precipitations with trichloracetic acid, followed by the microkjeldalh analysis of both supernatant solution and precipitate.[4] No nitrogen was found in the precipitate. Nitrogen in the supernatant solution agreed with total nitrogen determination. Protein nitrogen was also tested for by the tungstic acid precipitation method.[5] There was no precipitate.

2. *Sugar Content—Total Sugars: 1.08 mg. glucose/cc.*

Reducing sugars: 0.63 mg. glucose/cc.

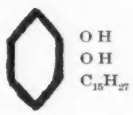
Non-reducing sugars: 0.45 mg. glucose/cc.

Determined by oxidation with ferricyanide and ceric sulfate titration.[2] (Chemists' note: "We know of no quantitative test for sugars that would distinguish between sugars and other oxidizable materials.")

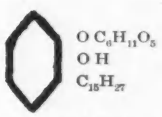
COMMENT

That the chemical analysis of Antigen No. 12 failed to show the presence of protein nitrogen was not surprising in view of the behavior of the allergic response in persons suffering with poison oak dermatitis, and the inability to elicit in such persons the positive corroborating tests usually associated with a true protein sensitivity. On the other hand, the large amounts of sugar which this fraction contains may be due to the presence of water soluble plant glucosides.

A few chemists who have made exhaustive studies with poison ivy extracts have differed in their conclusions regarding the nature of the active principle. Acree and Syme[1] for instance, concluded that the active principle of poison oak was "toxicodendrin," a glucoside of gallic acid, fisetin and rhamnose. McNair[3] on the other hand, working with poison oak, concluded that the active principle was a poisonous substance which he identified as a polyhydric phenol and which he named lobinol. The chemical structure of these two substances are quite similar, the difference being that in the glucoside a sugar radical replaces one of the hydrogens.



Lobinol



Toxicodendrin

In view of this similarity in chemical structure, plus the observations recorded in this article regarding the action of the several fractions of the poison oak extract on sensitized guinea pigs, could it be that the glucoside and not the vesicant is the immunity building fraction? And could it be that the vesicant, which is the potent fraction when taken by mouth, is changed by the hydrochloric acid in the stomach and/or conjugated with a sugar by the liver in order to make it antigenic?

As a precedent for entertaining such a concept, it has been shown that with certain other polysaccharides—for example the pneumococcus—the polysaccharides found in the capsule of that organism play a specific role in antibody production, with the subsequent formation of demonstrable specific precipitins and agglutinins.

Work with Antigen No. 12, however, met with disappointing results in this regard, for when using sera from guinea pigs immunized with this antigen, the author was not able to demonstrate the presence of precipitins in any of several tests made.

The author is convinced that the mechanisms involved in the building of immunity in animal

tissue, through the administration of poison oak antigens, are just as complex as are the chemical constituents of the plant itself. It would appear that what the problem needs is an immunologist and an enzyme chemist working together, in order to solve it satisfactorily.

SUMMARY

1. Poison oak extracts were made with four different solvents. Their solids content and their vesicant content were estimated and compared.

2. Sensitized guinea pigs were treated with these extracts by mouth and by intramuscular injection and their immunological results compared.

3. One of the poison oak extracts was separated into fractions which were then administered separately to sensitized guinea pigs. One fraction was found to be more efficient when given orally. Another was more efficient when given intramuscularly.

4. Several methods are described for obtaining the various fractions. The result of the chemical analysis of one fraction is given and its significance discussed.

The author is indebted to Dr. Troy Daniels, Dean of the College of Pharmacy, and to Dr. Hermann Somer, Chief Chemist at the Hooper Foundation of the University of California, for their interest and helpful suggestions during the course of this study; also to Miss R. E. Nell, who made the chemical analyses of Antigen No. 12.

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Correction

Part of the list of references for the article Typhus Fever in the Second World War, by J. C. Snyder, M.D., which appeared in the January, 1947, number of CALIFORNIA MEDICINE, was inadvertently omitted. The remainder of the list is printed below:

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Thiouracil in Thyroid Diseases*

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SINCE Plummer,[10] in 1923, introduced the use of iodine for preoperative preparation of patients in the treatment of hyperthyroidism, other methods of subtotally destroying the hyperplastic thyroid tissue have been employed less frequently and enthusiastically. Renewed attention has been paid to radiation therapy since the discovery of radioactive isotopes of iodine. Lately, pharmacologic studies on chemotherapeutic agents, the sulfonamides, have attracted the attention of many groups of workers in the field of thyroid disease, in the hope of finding chemical agents for the medical treatment of hyperthyroidism.

Mackenzie, Mackenzie and McCollum,[7] Richter and Clisby,[12] Kennedy[5] and Astwood and his associates[1] showed that sulfonamides and derivatives of thiourea inhibit the formation of thyroid hormone. Since publication of this work, many reports indicate that thiouracil is the most successful agent of the chemical compounds investigated, although propyl derivatives may be equally effective and less toxic.[2] There is now no doubt that thiouracil, in proper dosage, will inhibit formation of thyroid hormone in patients with toxic goiter and cause a remission in the symptoms of this disease as long as the drug is administered.

From the clinical standpoint, certain questions must be answered before thiouracil can be evaluated in the therapy of hyperthyroidism. In the preparation of patients for thyroidectomy, is thiouracil more efficient and safer than iodine? Does it take longer with thiouracil than with iodine to produce a remission? Are there greater dangers from toxic effects of thiouracil? Can this drug alone, without using methods for destruction of the thyroid gland, permanently inhibit the excess production of thyroid hormone? Is thiouracil effective only during the period of its administration?

PHARMACOLOGY OF THIOURACIL

The pharmacology of thiouracil has been best summarized by Williams, Kay and Jandorf.[14] Thiouracil is rapidly absorbed from the gastro-intestinal tract, an appreciable concentration being found in the blood within 30 minutes after administration. With divided daily doses totaling 0.2 to 1.2 grams, concentration in the blood varies from 0.8 to 6.4 mg. per cent. Most of the drug is in the cells in the blood stream. Excretion through the kidneys is rapid. Thiouracil is distributed through all tissues of the body and, according to Williams and his associates, is sometimes found in large quantities in bone marrow, thyroid, ovaries and pituitary while relatively small concentrations are found in striated muscle, testes and liver. These workers noted also that adenomata of the thyroid gland have a higher concentration of thiouracil than does normal thyroid tissue. Cerebrospinal, pericardial and edema fluids contain less thiouracil than whole blood; concentration in pleural and ascitic fluid is about that of blood and concentration in milk is three times that of blood. The drug is destroyed rapidly in the stomach and by contents of the small intestine. It is also destroyed by certain tissues of the body.

The exact mechanism of action of thiouracil on the thyroid is not known. The action is a direct one on this gland with suppression of hormone production. It has been postulated that the enzyme diiodotyrosinase is inhibited so that diiodotyrosine is not converted to thyroxin. Harington and Rivers[4] have shown recently that conversion of diiodotyrosin to thyroxin is almost entirely suppressed in vitro by sodium thiosulphate.

DOSAGE

In preoperative use of thiouracil, the best dosage seems to be between 0.8 and 1.0 gm. given in evenly divided dosages of 0.2 gm. each throughout the waking hours during the first two to three weeks. If the patient is not then ready for surgery, the dose should be decreased to a total of 0.6 gm. per day and at the end of another two weeks to 0.4 gm. per day. None of the patients under my observation has needed over 33 days of preparation for surgery, so a dose as low as 0.4 gm. has been given only experimentally. My experience has been that patients respond much better with 0.8 to 1.0 gm. daily than with small doses. With nonsurgical treatment of hyperthyroidism, the maintenance dose is 0.2 gm. daily to 0.1 gm. every other day.

Two recent reports[8,13] have presented the toxic effects in large series of patients. In one series of 1,091 patients, it was stressed that there is one potentially fatal complication of the drug, agranulocytosis, which was responsible for the five deaths that could be attributed to thiouracil. It should be emphasized that this fatality rate of one half per cent is approximately the same as the surgical mortality in recent years in clinics having a wide experience in thyroid diseases. Moore and his associates[9] have pointed out that 27 of 781 patients, or 3.4 per cent, developed a leukopenia (of 3,000 white blood cells or less) and that 19 of 1,091 patients, or 1.74 per cent, developed agranulocytosis. One fourth of all patients in this series with agranulocytosis died. Chart I shows the response of one patient to thiouracil. The first bout of fever, leukopenia and cervical lymphadenopathy ended after the drug was discontinued and penicillin was administered, but a recrudescence occurred coincident with a streptococcal wound infection some two and a half weeks later. Patients who have had

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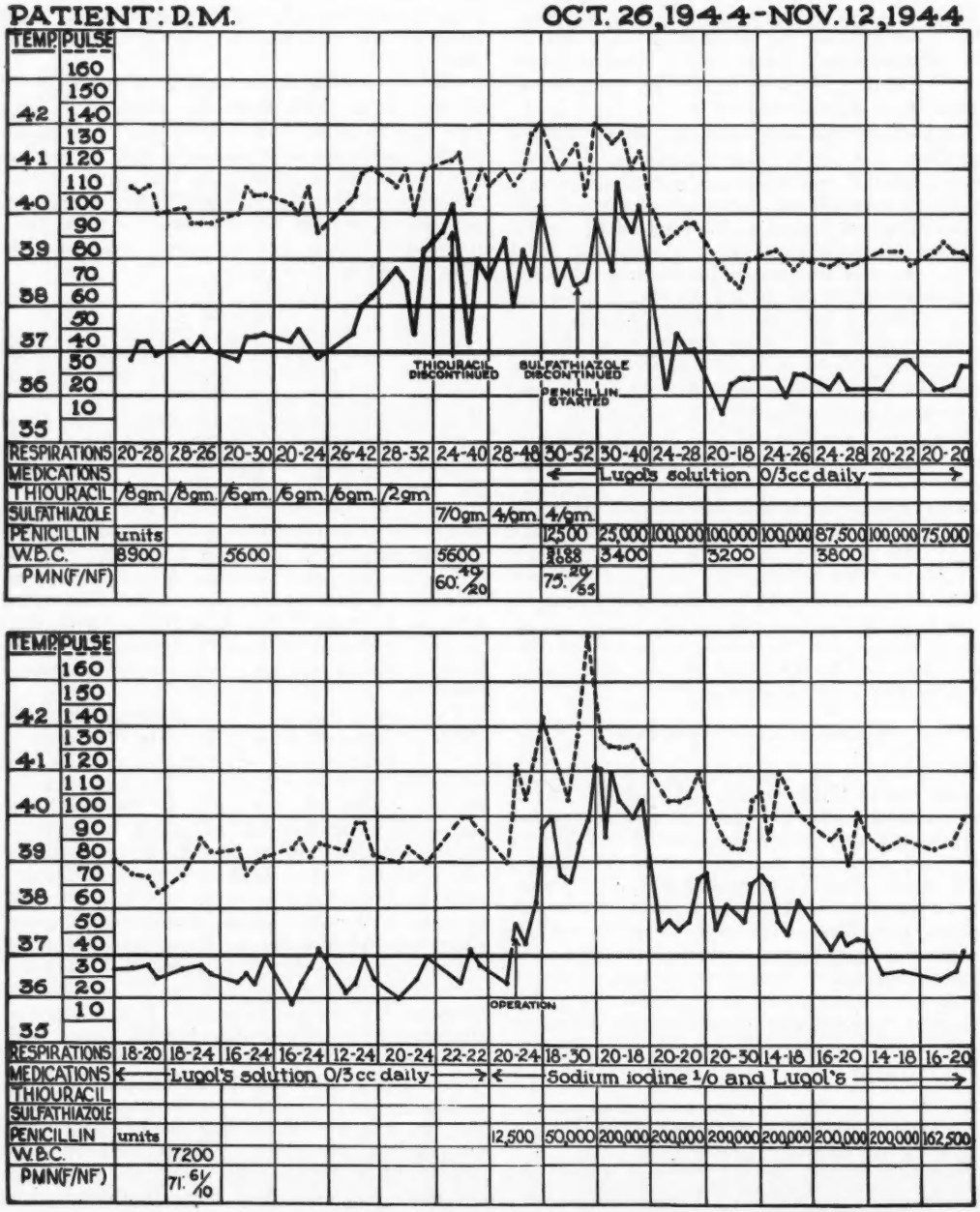
suppression of the function of the bone marrow are candidates for further such difficulties if any infection supervenes, even weeks after the original cause of the suppression has been removed. Leukopenia usually appears between the fourth and eighth week but it has been noted as early as the fifth day and as late as the fifth month during thiouracil therapy. To prevent any serious complications, a white blood cell count should be done repeatedly, preferably at least every third day, and

CHART I

THIOURACIL TOXICITY (FEVER AND LEUKOPENIA)



every day, if a trend toward leukopenia is noted. Intervals of three weeks or longer between counts should not be condoned.

Drug fever (Chart II) occurs in about 5 per cent of patients on thiouracil, and does not always indicate that the drug must be discontinued, although the experience at the University of California has suggested that most such patients no longer can tolerate this drug. About 5 per cent of patients have enlargement of lymph nodes and some of the salivary glands. Nausea and vomiting are encountered occasionally. Edema and myxedema have been reported. Skin rashes similar to those seen with sulfonamides are common. Hepatic damage has been noted.

The experience at the University of California Hospital has been that the postoperative course of really sick thyrotoxic patients has been smoother, with less fever and tachycardia, when these patients have received thiouracil preoperatively. On the other hand, when 3 to 5 grams of thyroid tissue are left *in situ* as is our custom in patients prepared in the usual manner with iodine, a much higher percentage have developed hypothyroidism even though thiouracil is discontinued within one to five days postoperatively. In fact, a third of our patients become hypothyroid, a figure that is about twice that of patients receiving iodine alone.

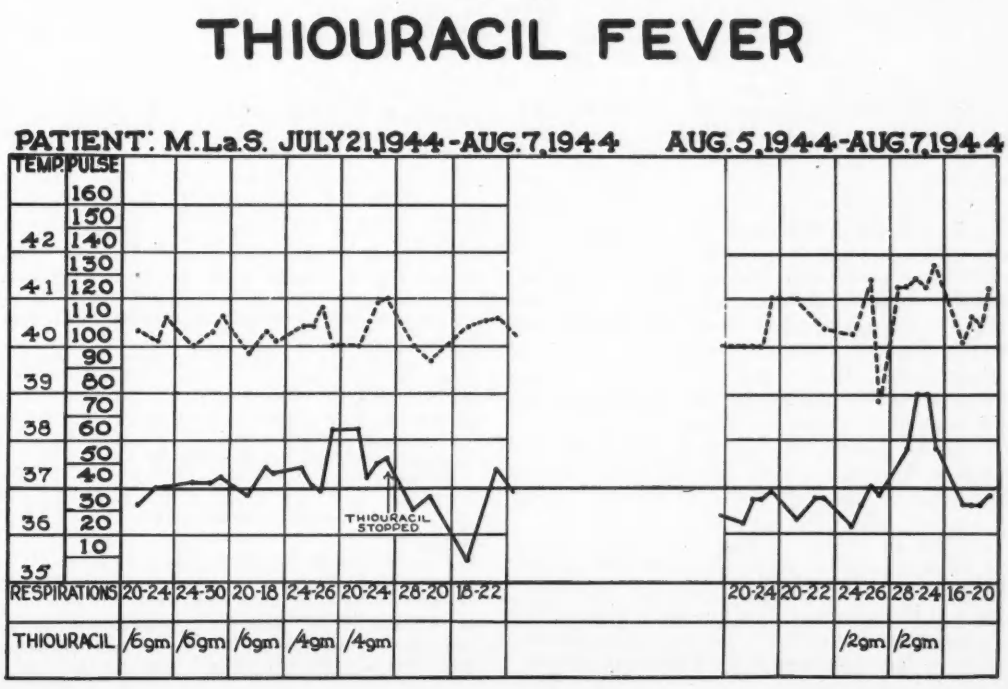
Only one of 41 patients in whom serial measurements of exophthalmos were made pre- and postoperatively showed a significant progression of exophthalmos. However, the patient with severer grades of exophthalmos is still not a candidate for thiouracil in spite of these reassuring figures since, according to the work of others, progression of exophthalmos has occurred during treatment with thiouracil.

PREOPERATIVE PREPARATION OF PATIENTS WITH THIOURACIL

Iodine produces a remission in Graves' disease by causing storage of thyroid hormone within the gland. The subsequent fall in basal metabolic rate and the clinical improvement that follows depend on the destruction and excretion of the excess thyroid hormone in the body; thus the rate of fall of the metabolism is similar to that of a patient following thyroidectomy, or to that of a patient with myxedema when thyroid therapy is stopped. If the administration of iodine—which, histologically, causes involution of the hyperplastic tissue—fails to produce this usual rate of fall in basal metabolism, it indicates, at least theoretically, that it has not been totally effective in damming thyroid hormone in the thyroid gland.

Thiouracil, by inhibition of hormone production, causes a fall in metabolic rate similar to that seen with iodine.[11,12] However, the thyroid gland, instead of involuting, becomes more hyperplastic. The delayed response in patients who have received iodine prior to thiouracil probably is due to the release of previously stored hormone. This means that the body must not only destroy and excrete the excess of thyroid hormone in its tissues but also that released from the thyroid gland with a consequently slower fall in the basal metabolic rate and slower amelioration of the clinical symptoms of hyperthyroidism. It should be mentioned that although half of our patients had been treated with iodine within a month prior to the use of thiour-

CHART II



acil, the average time between the start of therapy and operation under our care was only two days longer than in patients who had received no iodine.

Technical problems in surgical procedure arise because of the increased friability and vascularity of the thyroid gland of patients treated with thiouracil. Tissues are harder to handle and bleeding is more difficult to control. As one surgeon, H. Glenn Bell, phrased it: "Clamping a thiouracil-treated thyroid is like trying to put a clamp in a bowl of cornmeal mush." These technical problems can be avoided by the addition of iodine for one to two weeks prior to subtotal thyroidectomy.

At the University of California Hospital, we have not felt that thiouracil offers any advantages over iodine for the average patient with either a toxic diffuse or toxic nodular goiter. However, very sick patients with coincident ectopic rhythms and cardiac failure or very toxic patients who are in a severe exacerbation of hyperthyroidism and perhaps poorly controlled by iodine are excellent candidates for this drug. Of course, repeated leukocyte counts should be made and toxic effects should be watched for during preoperative preparation. All the other medical measures also should be used just as they are when iodine is given preoperatively. If thiouracil did not present the risk of serious toxic effects, it could be used in all cases rather than in selected groups.

Astwood[13] and many others have used thiouracil in the medical treatment of hyperthyroidism. There is no doubt from reports to date that a remission of symptoms will occur and can be maintained as long as small doses, such as 0.1 to 0.2 gm. daily, are given. The percentage of individuals in whom symptoms of hyperthyroidism recur when thiouracil is discontinued varies widely. Van Winkle and associates[10] report a minimum recurrence of 33.7 per cent, a figure that will almost certainly increase as hyperthyroid patients are observed for longer periods after thiouracil has been discontinued. No reports have stated specifically that thyroid glands return to normal size and consistency, which should also make one skeptical about "cures." The facts just stated, plus the expense of laboratory work and lack of evidence that hyperfunctioning thyroid tissue is permanently suppressed, suggest that thiouracil, as a single therapeutic agent in hyperthyroidism, will not long be used by experienced clinicians. This statement, however, does not apply to newer derivatives now being used experimentally.

King and Rosellini[14] have reported some success in thyroiditis from thiouracil. Thyroiditis which is subacute and not infectious in the sense that bacteria can be cultured from surgical speciments, responds to this drug. In such cases the patients have an enlarged, tender, firm, and spontaneously painful thyroid with local pressure symptoms, often fever, and an elevated sedimentation rate. There may be symptoms of hyperthroidism but usually only general irritability and lack of well-being. King and Rosellini state that thiouracil in doses of 0.2 gm. daily shortened the course of the disease in most of their patients. At the University of California Hospital, five of seven such patients seemed to respond favorably to thiouracil. An eighth patient, who did not respond at all, proved to have multiple hemorrhages in multiple nodules. Our experience indicates that dosage levels of 0.6 to 0.8 gm. per day may be more effective than the original dose of 0.2 gm., and that thiouracil must be continued for two to three weeks or longer.

SUMMARY

Thiouracil is a useful drug in preparation of thyrotoxic patients for surgical intervention when the hyperthyroidism is severe and complicated. It has not been proved better than iodine in moderate hyperthyroidism when used preoperatively. Thiouracil has not consistently produced a permanent remission in hyperthyroidism after the drug has been withdrawn. Nonbacterial (subacute) thyroiditis may respond to thiouracil therapy, although the reasons for this are far from clear. The most dangerous result of the toxic effect of thiouracil is agranulocytosis.

Grateful acknowledgment is made to the Lederle Company for the Deracil (thiouracil) used in our studies.

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Improved Forms of Insulin: Advantages Of Modified Protamine Zinc Insulin*

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IN the treatment of diabetes mellitus, objectives may be listed under six chief headings: (1) to relieve symptoms; (2) to maintain normal nutrition; (3) to prevent acidosis and thus coma and death; (4) to prevent excessive hyperglycemia (and glycosuria); (5) to prevent complications, and (6) to permit the development of the greatest possible carbohydrate tolerance.

The accomplishment of these aims requires knowledge on the part of the physician and cooperation on the part of the patient over a period of many years. The most advantageous use of insulin in the maintenance therapy of each patient, and the proper diet are the two tools most important in accomplishing the objectives in therapy.

The majority of students of the disease are agreed that the more nearly normal the blood glucose values are throughout the day, the greater are the chances to keep the diabetic patient in an optimal state of well-being. Regular insulin caused wide fluctuations in blood glucose levels and required multiple injections. Therefore, various slowly acting types of insulin were tried, and protamine-zinc insulin was emerged as the most widely used form for maintenance therapy. It was hoped that a single injection daily of protamine-zinc insulin would suffice to establish good control in the great majority of cases.

This hope has not been realized. Only the milder cases (usually those requiring 40 units or less daily) can be well regulated with protamine-zinc insulin alone. The present market form of protamine-zinc insulin is entirely a precipitate which is slowly absorbed over a period of 24 hours or more. In mild cases, in which the rise in blood sugar after meals is not great, such an insulin may prevent hyperglycemia during the day as well as during the night. In severe cases, however, it is usually not possible to give enough protamine-zinc insulin to control the blood sugar rise after food intake without causing nocturnal hypogylcemia. Such hypoglycemia does not occur "because protamine-zinc insulin acts strongest at night" (an overworked and inaccurate cliche), but because of the failure to take food at regular intervals during the night. If the patient ate regularly every four hours day and night, protamine-zinc insulin, because of its slow, constant activity, should prove ideal.

Of 350 well-controlled diabetic patients we have treated in the past four years, only 186 (53 per cent) could be regulated with protamine-zinc insulin alone, while 164 (47 per cent) required in addition a separate morning injection of regular insulin. Of the 186 patients well regulated with protamine-zinc insulin alone, 177 (95 per cent) required 40 units daily or less (average 26 units). Those patients requiring separate morning injections of the two insulins were the more severe diabetics, 148 of the 164 needing over 40 units daily, the average total dose being 55 units. It seems evident, therefore, that some different modification of insulin will prove necessary if we hope to control with one daily injection the majority of moderate and severe cases as well as the mild ones.

For practical purposes a compromise or combined form of insulin therapy is often very satisfactory: two separate injections are given each morning, one of protamine-zinc insulin (P.Z.I.) and one of regular (R.I.). Usually the amount of P.Z.I. needed is about three times as large as the dose of R.I. required, and the patients receive P.Z.I. 45 units, R.I. 15 units, or P.Z.I. 60 units and R.I. 20 units, etc. Although this is probably the best plan which is possible with the present market forms of insulin for patients with severe diabetes, it is far from ideal. Two injections daily are necessary, and patients often become confused with the two different types of insulin and two different sized doses.

Efforts to devise an insulin which, with a single injection daily, would establish good regulation in severe as well as mild cases have taken several directions: (1) proteins other than protamine, such as globin and histone, have been combined with insulin; (2) protamine-zinc insulin has been modified by varying its protamine and zinc content, and by changing the pH.

Histone-zinc insulin and globin-zinc insulin have been rather thoroughly studied. Neither of these modifications has given both the rapid effect and the prolonged activity desired.

MODIFIED PROTAMINE-ZINC INSULIN: COMPONENTS AND ACTIVITY

Modified protamine-zinc insulin (M.P.Z.) was at first made in our own laboratory but is now supplied for investigative purposes by the Eli Lilly Research Laboratories.* Approximately 75 per cent of this modified protamine-zinc insulin is in precipitated, slowly absorbed form, while 25 per cent is in solution and is rapidly absorbed. It contains

* Read before the Section on General Medicine at the Seventy-fifth Annual Session of the California Medical Association, Los Angeles, May 7-10, 1946.

From the Department of Internal Medicine, University of Southern California School of Medicine, and the Shelton Clinic, Westwood.

* Under the designation: Special Modified Protamine Zinc Insulin NP 50.

Figure 1

CHARACTERISTICS OF INSULINS STUDIED

Insulin	pH	Source of added protein	Solubility	Composition per 100 unit	
				Added protein	Zinc
				mgm.	mgm.
Modified protamine zinc	7.2	Salmon sperm	Turbid	0.50	0.1
Market protamine zinc	7.2	Salmon sperm	Turbid	1.25	0.2
Clear (acid) protamine zinc	3.4	Salmon sperm	Clear	3.8	0.3
Histone zinc	7.0	Thymus	Turbid	3.2	0.2
Globin zinc	3.7	Beef blood	Clear	3.75	0.3
Regular	3.0	None	Clear	None	0.02
Crystalline	3.0	None	Clear	None	0.02

Note: Modified Protamine Zinc Insulin contains half the added protein and half the zinc present in market PZI. It has about 75% slow effect and 25% rapid effect, the ideal proportion as found when separate daily injections of regular insulin and PZI are used.

approximately half of the protamine and zinc present in market P.Z.I. and is adjusted to pH 7.2. (Figure 1.) The reason for choosing a modification with 75 per cent slow effect and 25 per cent rapid effect was that in our own moderately severe and severe diabetic cases we were using P.Z.I. and regular insulin in separate morning injections and in the great majority of cases the proportion giving the best control was P.Z.I., 3 to regular, 1. The steps leading to the designing of modified protomine-zinc insulin has been reported previously.[4,5] In addition to our studies, observations of others treating diabetic patients led to the belief that an insulin with such proportionate effects would be the most widely useful. Joslin,[3] for example, found that more than 50 per cent of a series of patients required separate morning injections of P.Z.I. and regular insulin, the average doses being 39 units P.Z.I. and 13 units regular (proportion exactly 3:1). Assays upon patients[4] and upon rabbits[7] have demonstrated that approximately 75 per cent of the M.P.Z. insulin action is slow (like P.Z.I.) and 25 per cent is rapid (like regular insulin).

It is important to emphasize here that M.P.Z. insulin cannot be made extemporaneously by mixing P.Z.I. and regular (or crystalline) insulin. Although mixing equal parts of P.Z.I. and regular insulin will result in a preparation containing approximately half the protamine and half the zinc in P.Z.I., the pH will be near 5, at which all the contained insulin is precipitated. Control of the pH by proper buffering is necessary.

Modifications of protamine-zinc insulin containing only a half or a third as much protamine as market protamine-zinc insulin have given the most encouraging results. Two types of insulin with such lower protamine content have been suggested: (1) The biphasic insulin described above, which has been designated "M.P.Z. insulin" by MacBrdye;[4,5] and (2) a monophasic insulin in which all of the hormone is precipitated. The precipitate, however, is saturated with insulin and there is no excess protamine, so that the hormone is more quickly released than from standard P.Z.I., which contains a large excess of unsaturated protamine. This is essentially the product obtained by mixing crystalline insulin with P.Z.I. in the proportion of 2:1, as suggested by Colwell.[1]

GLOBIN-ZINC INSULIN UNSATISFACTORY

In 16 direct comparative case studies[6] it was found that modified protamine-zinc insulin gave better control in 13 patients than globin-zinc insulin, while only three diabetic patients were equally well controlled. In no case did globin-zinc insulin establish better regulation than modified protamine-zinc insulin. Globin-zinc insulin did not prevent after-breakfast hyperglycemia in 12 of the 16 cases

and caused afternoon hypoglycemia in nine of the 16. (Figure 2.) Fasting blood sugars were higher in 13 of the 16 cases when globin-zinc insulin was used. Even when special diets were employed, allowing a smaller breakfast and a larger lunch, the same defects in control were observed with globin-zinc insulin. A mid-afternoon feeding was not given in any of these studies because it was considered illogical and impractical.

SUPERIOR CLINICAL RESULTS WITH M.P.Z. INSULIN

There have been several comparative clinical studies of the suggested new insulin modifications. Peck[8] obtained good results both with the modified protamine-zinc (M.P.Z.) insulin and with a 2:1 crystalline-P.Z.I. mixture, the comparative figures being somewhat better with the former. Del Fierro and Sevringhaus[2] established good control in 15 of 17 cases with M.P.Z. insulin and found it superior to P.Z.I., globin-zinc insulin or mixtures.

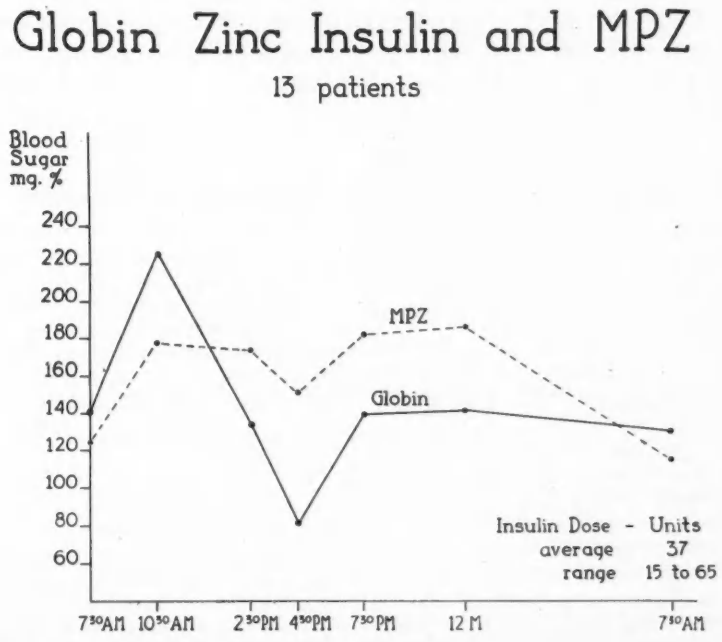
MacBryde and Reiss[6] compared M.P.Z. insulin with the 2:1 mixture in a series of ten severe cases and reported better 24-hour blood sugar curves in every case with the M.P.Z. insulin. Irregular results were obtained with the mixture, with failure to duplicate 24-hour curves. In general the rise in blood sugar after breakfast was poorly controlled with the mixture and there was a tendency to hypoglycemia at midafternoon or midnight. (Figures 3 and 4.) In a total of 110 case studies conducted over a four-year period, good regulation was established in 98 patients (90 per cent) with a single injection of M.P.Z. insulin daily. Severe as well as mild cases were well controlled, 64 per cent of the well-regulated cases requiring over 40 units daily, some as high as 120 units (average 73 units).

At the present time evidence seems to indicate that protamine-zinc insulin, modified by a considerable reduction in its protamine content, will in one of its forms, prove to be the preferable insulin for maintenance therapy. It would seem logical that a biphasic insulin could best control both the hyperglycemia following meals and the constant glycogenolysis demanding a small but steady supply of insulin every hour of the day and night.

CONCLUSIONS

1. An ideal insulin for maintenance therapy of diabetes should:
   a. Be effective for at least 24 hours, so that a single morning injection is sufficient.
   b. Have rapid enough initial activity to control the blood sugar rise after breakfast, plus sufficient prolonged activity to prevent hyperglycemia at night.
   c. Exhibit a pattern of activity not requiring special or abnormal diets, but permitting normal distribution of carbohydrate at the meals, and allowing normal meal hours.

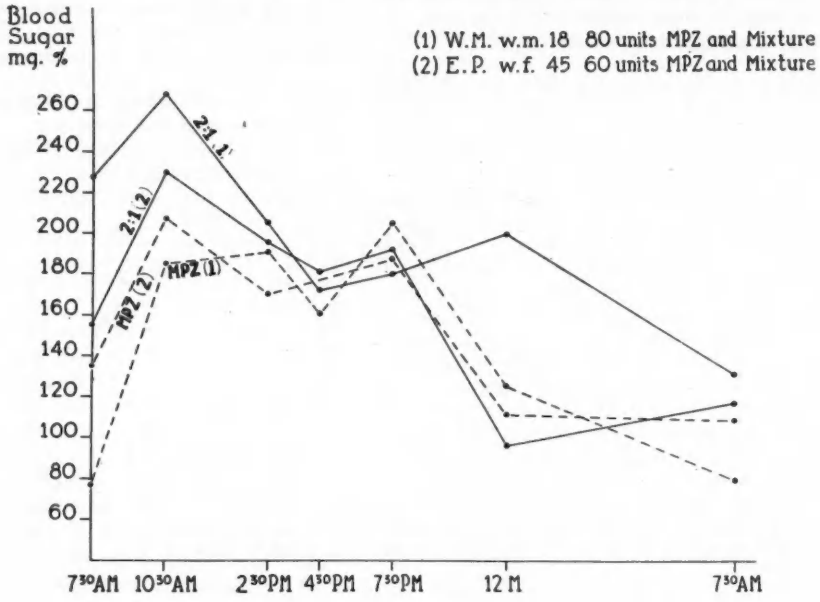
Figure 2



Note: (1) Globin insulin did not prevent after breakfast hyperglycemia.
(2) Globin insulin caused hypoglycemia (below 70 mg %) in 6 of the 13 cases at 4:30 PM.
(3) MPZ prevents after breakfast rise, causes no hypoglycemia.

Figure 3

MPZ Insulin Compared with 2:1 Mixture Studies on 2 Typical Cases



Note: 1. Mixtures gave irregular, unpredictable results. 2. In direct comparisons on 10 patients requiring from 45 to 115 units (average 73 units) daily, MPZ Insulin gave better control in every case than 2:1 Mixture.

d. Not cause hypoglycemia.

e. Reproduce as nearly as possible a normal type of 24-hour blood sugar curve.

f. Be satisfactory for regulating patients requiring the larger doses (over 40 units daily) as well as for patients with smaller insulin requirements.

2. Of all the insulins studied, modified protamine-zinc insulin most nearly fulfills these requirements.

3. The use of multiple forms of insulin should be discouraged. Good therapy of diabetes requires simplicity. Globin-zinc insulin does not satisfy the requirements for an insulin of intermediate activity, and its introduction on the market has unfortunately added to the confusion in this field.

4. The use of variable extemporaneous mixtures, perhaps a necessary step in furthering our knowledge, has also added to the confusion. Since 90 per cent of a series of 110 diabetic patients were well regulated with modified protamine-zinc insulin, there seems to be no necessity for prescription of individual insulin mixtures.

5. The 2:1 crystalline-P.Z.I. mixture did not give a good, predictable, intermediate type of response.

6. Two forms of insulin should be sufficient: (a) modified protamine-zinc insulin such as that used in these studies which might well be substituted on the market for standard protamine-zinc insulin, since it will control a very much larger percentage of patients with uncomplicated diabetes; and (b) regular (or crystalline) insulin for use in diabetic emergencies and whenever supplementary insulin is required.

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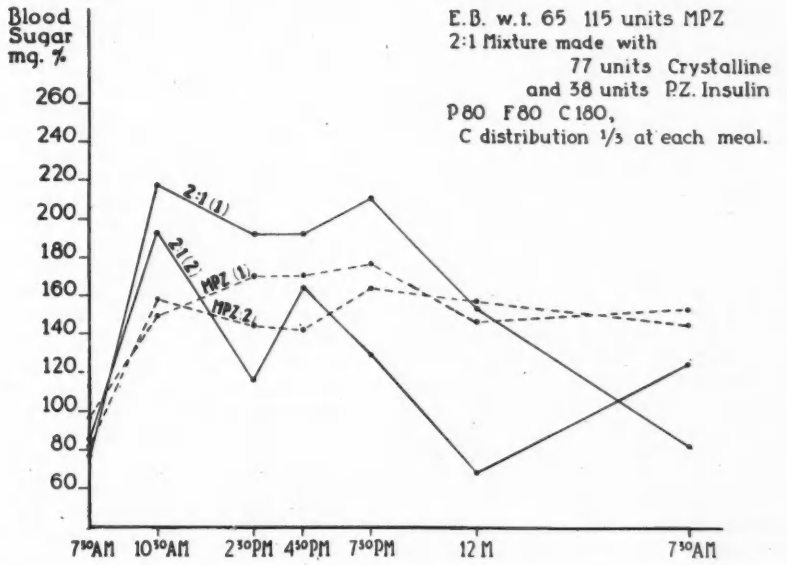
Figure 4

Mixtures Give Irregular Results
MPZ compared with 2:1 Crystalline-PZI Mixture
2 successive 24 Hour Curves on the same patient



Note close similarity of MPZ curves, great divergence of mixture curves.

Guest Speakers, C.M.A. 76th Annual Session
Los Angeles, April 30—May 3, 1947

A. W. Oughterson, M.D., *Medical Director*, American Cancer Society, New York City	"Planning the Attack on Cancer" "The Diagnostic Problem in Gastro-Intestinal Cancer"
Hobart A. Reimann, M.D., *Professor of Medicine*, Jefferson Medical College, Philadelphia	"Virus Pulmonary Diseases," "Periodic Diseases" "What's New in Infectious Diseases"
James T. Priestley, *Mayo Clinic*, Rochester, Minnesota	"The Surgical and Physiological Aspects of the Treatment of Duodenal Ulcer"
Albert Snell, M.D., *Professor of Medicine*, Mayo Foundation, Rochester, Minnesota	"The Management of Infectious Hepatitis" "What's New in Gastroenterology"

MEDICAL PROGRESS:

Recent Advances in Neurology

CHARLES D. ARING,* M.D., *San Francisco*

SINCE presidential addresses before two national neurological societies in 1946 were concerned with it, we may note at the outset that neurology is not psychiatry, though there are medical forces which would encourage this confusion. While a neurologist may know something about behavior, normal or abnormal, it is quite safe to say that it is not because of his knowledge of the structure and function of the nerves, spinal cord, and brain. What information we have about the physical universe and particularly of the intricate structure, function, and disease of the brain tells us little or nothing of human behavior; it throws no light on why one person is quietly and meekly passive and another boisterously aggressive, nor why either of them may or may not achieve, and what motivates the criminal and the saint, nor will it do so for centuries to come. In 1870 Doctor Oliver Wendell Holmes[14] said on this subject, "We do not find Hamlet and Faust, right and wrong, the valor of men and the purity of women by . . . examining fibres in microscopes." A neurologist is not necessarily the sort of expert in human affairs that many expect him to be and it is well to have done with this notion, particularly before a discussion concerning progress in neurology is attempted. The neurologist's information other than intuitive about mental functioning, as one should expect, is directly related to his training therein, in other words to his study of psychiatry.

A neurologist is one who is familier with the function and malfunction of nerves, spinal cord, and brain, which to be sure, like malfunction of the heart, lungs, or liver may result in mental symptoms. Besides, neurology has come to include certain disorders of the muscles and endocrine glands. Within the last 50 years the neurologist has been joined by his colleague, the surgeon, who is technically expert in manipulating these tissues. They alleviate certain diseases between them, for example, infections and growths within the skull or spinal canal; the neurologist, however, takes precedence in his interest in certain other disorders of the nervous system. As an example, we may cite epilepsy and cerebral hemorrhage.

EPILEPSY

The meetings of the Association for Research in Nervous and Mental Disease on December 13 and 14, 1946, in New York City were concerned with the topic of epilepsy. For anyone interested in the latest knowledge of this subject the proceedings‡ of this meeting are a requisite, since epilepsy was considered exhaustively in all of its phases. Parenthetically, these monographs which appear annually are among the best neurological literature extant.

Lennox's[18] observations have been corroborated regarding tridione as an effective drug in the therapy of petit mal epilepsy. It is dispensed in capsules each containing 0.32 Gm. (5 grains) and dosage has varied from 1.0 to 2.0 Gm. (15 to 30 grains) a day without much regard for age. Since there is little other therapy that is successful in petit mal, it is important to know about tridione.

Mesantoin (methylphenylethyl hydantoin) while not quite as effective as dilantin sodium in the treatment of grand mal epilepsy and psychomotor seizures, is an anticonvulsant drug useful in those patients who exhibit untoward reaction to dilantin such as uncontrollable ataxia or gum hypertrophy. Drugs of the hydantoin group should be begun in a single daily dose of 0.1 Gm. (1.5 grains) after food for about three days, then the dose is increased by one capsule weekly until the seizures are brought under control. The usual minimal effective daily dose of mesantoin, as dilantin, is three capsules (0.3 Gm.) and the usual maximum daily dose is 0.6 Gm. These drugs are administered best after meals because of their potentiality of otherwise producing gastric distress.

The excellent program of public education in epilepsy under the direction of the American Epilepsy League gains momentum. This is a most important and enlightened development. Patients should be urged to join this organization† and receive carefully edited literature* bearing on their condition. This is a practical necessity in the modern therapy of epilepsy since many questions occur to the patient about his disease that the physician cannot hope to answer. All aspects of epilepsy are considered in these books and pamphlets which are written in language that may be understood by the patient.

It is becoming clear with widening experience that the incidence of psychomotor epilepsy is consideraly higher than had been thought to be the case previously. Evidently this type of epilepsy has been confused in the past with petit mal which occurs rarely in the adult. Any person experiencing rather short episodes of unusual behavior for which he has no memory might well be suspected of suffering from attacks of psychomotor seizures. It should never be forgotten that homicide has been

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‡ Epilepsy. Res. Publ. Ass'n. nerv. ment. Dis., volume 26. Baltimore, Williams and Wilkins Co. 1947. (In press.)

† American Epilepsy League, Room 405, 50 State Street, Boston, Massachusetts.

* e.g., Lennox, W. G.: Science and Seizures: New Light on Epilepsy and Migraine, New York, Harper and Brothers, 2 ed., 1946.

Yahres, H.: Epilepsy—The Ghost Is Out Of The Closet. Published by Public Affairs Committee, Pamphlet No. 98, New York City, 1944.

committed during attacks of psychomotor epilepsy. It is of extreme importance to make this diagnosis correctly since the disorder responds so nicely to dilantin or to phenobarbital, properly administered.

ELECTROENCEPHALOGRAPHY

With increasing experience it has become apparent that electroencephalography is not a tool to be used frequently in diagnosis;[8] rather it is a method of investigation. Possibly the most important diagnostic use of the electroencephalograph occurs when epilepsy is suspected and proof thereunto is badly needed. Then serial electroencephalographic studies done every second or third day may reveal cerebral dysrhythmia, since it has been demonstrated that the electroencephalogram is considerably more apt to be abnormal immediately before, during, and immediately after a fit than it is during the remainder of the interseizure period. At the recent meetings in New York, Frederic and Erna Gibbs[11] reported that cerebral dysrhythmia in patients suffering from epilepsy may be demonstrated in almost 100 per cent of the cases if records are made when the patient is asleep.

NEUROSYPHILIS

There is no longer doubt about the effectiveness of penicillin in the therapy of many types of neurosyphilis.[31]** It should be administered in doses of 50,000 units intramuscularly every three to four hours day and night until about 5,000,000 to 10,000,000 units have been received. At present it seems well to follow a course of penicillin with the older types of therapy; fever therapy may be administered simultaneously with or subsequent to penicillin.

A second course of penicillin has been followed by favorable results in some cases of neurosyphilis where the first course had had little effect.

CEREBRAL COMPLICATIONS OF PNEUMONIA

Baker and Noran[1] have been studying experimentally the encephalitic complications of pneumonia after finding numerous intravascular clots or thrombi in the brains of persons dying with the disease. They noted that 8 cc. of a solution of finely homogenized lung tissue injected intravenously in animals of the same species was followed promptly by convulsions and death. Homologous extracts from organs other than the lung proved innocuous as did lung of heterologous species of animals. The brains from the animals succumbing to the lung inoculations consistently revealed intravascular clots and perivascular damage. These workers believe that the pathologic picture in the brain of the experimental animals is identical to that which they found so commonly in cases with the encephalitic complications of pneumonia.

Baker and Noran noted that the encephalitic symptoms appeared at the beginning of, during, or after the pneumonia during convalescence. They feel that the cerebral lesions probably are due to some change in the clotting mechanism since in all animals all symptoms could be prevented by a preliminary intravenous injection of 100 units of heparin. This work may bear on the pathology of disseminated sclerosis, as Putnam[24] has brought forward evidence concerning intravenous clotting in this disease.

EXTINCTION OR SUPPRESSION PHENOMENON

The neurological examination may be briefly defined as a comparison of the form and functions of one side of the body with those of the other, and of the functions of the patient with those of the examiner. We must now add that simultaneous testing of the two sides may be necessary.

In a series of closely reasoned presentations, Bender and Teuber[3,4] and later Reider[26] have studied the phenomenon termed variously as suppression or extinction, in brain-wounded military personnel. They have demonstrated that certain signs of neurological damage may be brought out only by making the cerebral hemispheres compete simultaneously. One may test a certain sensory function, for example touch or pain, in the usual manner, first on one side of the body then on the other and determine it to be normal. However, by testing touch or pain simultaneously on the two sides it may be shown that the side of the body served by an injured cerebral hemisphere may demonstrate certain deficits in sensory appreciation. Possibly this may be most readily demonstrated in the fields of vision where with the usual perimetry and screen techniques the visual fields may be considered to be normal. Yet simultaneously presented objects in both visual fields may result in fading of the object in the field subserved by an injured lobe. This phenomenon was termed "visual inattention" by older neurologists who recognized it as a precursor to the visual field defect in progressing disease.

FASCICULATION OR "FIBRILLATION" OF MUSCLE

Particularly to reassure the seemingly numerous physicians who occasionally suffer from muscle fasciculations, mention should be made of the benign form. Before doing so, however, it should be noted that the muscle fasciculation that accompanies the inexorable advance of amyotrophic lateral sclerosis is not benign; on the contrary it is a most ominous portent. However, it usually is not found by the patient; as a rule he is unaware of its existence until it is called to his attention by a physician.

Benign muscle fasciculation[10] is of reasonably frequent occurrence, particularly toward the end of the day when fatigue is maximal. This type of fasciculation usually limits itself to a single muscle and the movement is somewhat coarser than that acompanying gradual muscle and anterior horn cell deterioration, and it usually disappears after a night's sleep. I have observed cases of benign muscle fasciculation in which certain muscles, particularly those of the calves, are continuously in small movement which has been so aptly described

** See the series of articles on the therapy of various types of syphilis with penicillin, which appeared in the January 4, 1947, issue of the Journal of the American Medical Association.

as resembling that of a bag of worms. This phenomenon continues for years and is innocuous except as it annoys.

Fasciculation of muscles may be observed in disorders of the peripheral nerve.

PSYCHOSOMATIC DISORDERS

A most significant article by Halliday,[12] a doctor of public health in Glasgow, has recently appeared with an analysis of the factors responsible for the upward trend of psychosomatic organic affections. Using epidemiological techniques, Halliday has given the first clear indications why we are being inundated with psychosomatic disorders in this era, and he also gives reasons why hysteria is becoming a rarity. This contribution is of such timeliness that it should be read by every physician, since each of us is faced daily with some aspect of these disorders.

As for the neurologist, one need only survey his practice to find irrefutable evidence that he should have an orientation to psychiatry. By far the great majority of patients who come to the neurologist are those whose illnesses stem from emotional disturbance. If the neurologist handles these people without psychiatric insight, his practice is doomed to futility. Both his practice and his increasing concern with chronic disease leave the neurologist no choice but that of understanding and utilizing modern psychological concepts.

An increasing number of disorders previously thought to be of neurological origin primarily, are responding to psychotherapy properly administered,* and there are indications that the list will be lengthened with the passage of time. Many of the chronically painful syndromes such as headache, the neuralgias, myalgias, causalgias require psychological insight, since it must be obvious to us that persons react differently to various noxae. It should be clear that there must be reasons for such differences and that they might best be sought for in the psychological sphere.

Migraine: The syndrome of migraine is seemingly being widened to include many chronic painful conditions about the head and neck and shoulders, including the ubiquitous atypical facial neuralgia.[36] It is quite certain that migraine is a protean disease, that its manifestations are myriad.

Recent work[28] has gone far toward proving the prescient doctrines postulated so long ago by Latham[17] which briefly stated are that the initial symptoms of migraine are the result of spasm of intracerebral blood vessels and that the headache itself is due to dilatation of vessels in the scalp. In 1872 Peter Wallwork Latham, then Downing Professor of Medicine at Cambridge, noted further that "sufferers from migraine possess what is called the nervous temperament, their brains are excitable, their senses acute and their imaginations free. The attacks are induced by . . . strain of the feelings, such as grief, anxiety . . ."

We have learned, slowly to be sure, that Doctor Latham's hypotheses are valid. Sufferers from migraine, as he clearly enunciated, fit into a personality pattern. They are neat, meticulous, efficient, and orderly people who, despite their facade of quiet, good nature are subconsciously disturbed by their less fussy and less efficient fellow men. When the person suffering from migraine is helped to become cognizant of the trivial environmental happenings which upset him, he may then be able to prevent the occurrence of some if not all of his disabling attacks, a prevention which surpasses many of the symptomatic forms of temporary relief.

Post-Traumatic Syndrome: For an excellent statement of reasons for the steady increase in automobile accidents, reference should be had to an article by Evans.[9] Here is a problem in which medicine will soon have to take a hand; as Evans has noted, rightly we think, such a state of affairs would not continue unless it gratified something pretty deep in the national psyche.

Studies of post-traumatic headache[30] are clarifying this quite common disorder. Simons and Wolff[32] have pointed out that the danger of threats to the integrity of the head because of the implications concerning "brain" initiative, alertness and intelligence in our society, jeopardize the security of the moderately insecure and undermine the poorly adjusted. Associated emotional reactions are accompanied by physical changes in skeletal muscles (sustained contraction) and blood vessels of the scalp that result in headache. The occurrence of headache arouses fresh anxiety and convictions of impending catastrophe.

The attitude of the physician caring for patients with acutely injured heads is of manifest importance as regards recovery. The fearful, overly cautious physician who betrays his insecurity by requiring immobility for weeks and months following injury, aids and abets his legal brethren who prevent the clearing away of the legal aspects of the situation until it may be determined just how badly off the patient may become. This chasing-the-rainbow technique results in nothing so much as frustration. The possible loss in quick financial settlement will never in any case outweigh the devastating effects of prolonged illness of increasing severity which almost invariably are engendered by these methods.

An indisputable fact that the physician and particularly the surgeon cannot afford to neglect is that the prevention of chronic post-traumatic headache is more readily attainable than its cure. Reassurance and interpretations in the acute stage often allay anxiety so that head sensations assume

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* One often is asked to explain how psychotherapy is done, the questioner obviously expecting to try it at the next opportunity. One may as well expect to remove a brain tumor or a foreign body from a bronchus after a few kind words. While it is true that most contacts between physician and patient contain in them elements of psychotherapy, such cannot be expected to effect any but the most superficial of emotional disturbances. A neurosis in development for decades may not be expected to be superficial, and is no less difficult of eradication than many another disease of long standing. (The reader is referred to the book on the subject by Franz Alexander and Thomas French, "Psychoanalytic Therapy. Principles and Applications." Ronald Press Co., N. Y.) However, it seems quite certain that if we are to stem the mounting tide of psychogenic disorders, the general practitioner of medicine has got to learn something about effective psychotherapeutic techniques. It goes without saying that the modern student of medicine should know about them at the time of his graduation.

dwindling significance; probably the most important reassurance is the attitude of the physician who gets the patient out of bed early and who, having justly weighed the situation, minimizes the significance of the symptoms.

Probably next in importance is an evaluation of the setting of the accident. If it occurred in a setting of anxiety, resentment and frustration in a person with long-standing maladjustment, the prognosis is obviously unfavorable, particularly since such persons are prone to indulge in what might be termed nugatory fiddling of the legal variety. If there has been no great personality disturbance prior to the accident and the patient understands the place of the accident and its attendant emotions in his entire life situation, it is reasonably certain that the prognosis is good.

Vascular Diseases: If the emotions are able to effect certain transient changes in blood vessel calibre* in migraine, there is every reason to expect that blood vessels in other areas may respond similarly, and indeed relief has been obtained in vasospastic disorders of the extremities by psychotherapy.[22,35] Analogous therapeutic endeavor has been effective in some cases of arterial hypertension,[5] presumably before a state of irreversibility has supervened. Certain reactions within the nose accompanying emotion[15] probably fall within this category of behavior.

Central angiospastic retinopathy has been reevaluated[13,37] in light of its occurrence in young military personnel. It has been shown that under the tension of battle irreversible changes may occur in the retina due to spasm of retinal vessels induced emotionally.

Aphasia: The relief of dysphasia in brain injured soldiers with the use of sodium amytal has been reported by Linn and Stein.[21] They demonstrated that men who had suffered injury to the left cerebrum and who were practically mute could be made to talk under amytal, presumably when certain of their anxieties were relieved with this drug. Such improvement as could be effected with amytal was sometimes maintained in the postsedative period. A report on this technique in civilians who sustained dysphasia during stroke will appear shortly. It is thought if one does not obtain a change with the first amytal interview, subsequent interviews may be effective.

Narcolepsy: This condition which has been considered to be due to some undemonstrable disturbance about the diencephalon finally has been clarified.[16,33] While these attacks of irresistible sleep may be prevented by the use of benzedrine, it may be possible to effect a cure with psychotherapy. Persons suffering from narcolepsy have been shown to escape temporarily into short attacks of sleep from what to them amount to episodes of otherwise insoluble conflict.

Causalgia: There have been several reports in the recent literature[20] on the relief of causalgia by psychotherapy. Causalgia is an intense burning pain which follows in the wake of partial injury to peripheral nerves, particularly those of the extremities, which is worsened by stimuli of almost any variety, even certain sounds accentuate this unbearable pain. The most successful therapy up to now has been blocking appropriate sympathetic ganglia with procaine and/or alcohol.

Painful Phantom Limb: The relief of painful phantom limb by shock therapy has been reported by Pisetsky.[23] Practically all persons who sustain an amputation experience what is called a phantom in that it feels as though the amputated extremity is still a part of the body. Occasionally such a phantom is painful, and such pain has been notoriously unrelievable, although in one instance an extirpation of an appropriate portion of the contralateral parietal lobe[7] afforded relief.

Accumulating experience suggests that extremely chronic, intractable pain of a certain type may be relieved by electric shock therapy. For how long, is not known. This offers an avenue to the psychotherapeutic approach, since patients are not fit subjects for psychotherapy while suffering from extreme pain. Sometimes with the application of a single shock, it is possible to relieve the pain and then proceed with psychotherapy which had been previously inapplicable. Obviously such an approach is not required where other methods of relief are apt to be rewarded with improvement. It is to be reserved for those carefully evaluated patients in whom it has been determined that there is a large psychogenic element.

It is of some interest that prefrontal lobotomy has also been used in the relief of chronic intractable pain of physiogenic and psychogenic varieties. Parenthetically this procedure has resulted in what appears to be permanent relief of vascular hypertension.

THE ACTION OF PLACEBOS

While on the subject of relief of pain the important article by Batterman[2] on the evaluation of analgesic drugs may be noted. Careful studies have demonstrated that regardless of the severity of pain or the underlying organic disease, placebos will result in analgesia in approximately 40 per cent of trials. What is more a patient may be addicted to a placebo and demand its continuous administration.

These effects of placebos demonstrate how utterly futile it is to rely on a drug in the differentiation between psychogenic or physiogenic disorders. Such studies also suggest that we may question the results of those persons who, when testing a supposedly significant substance, control it by the administration of an indifferent substance, noting that the indifferent substance had *no effect whatsoever*. In such tests placebos should have a modicum of effectivity. There is more to the administration of a substance than those mechanistic concepts that have mostly prevailed up to now, would have led us to believe.

CHRONIC DISEASE

Neurology has become almost imperceptibly a science of chronic disease,[29] largely because the more acute diseases of the nervous system have

* An everyday experience is blushing.

been adeptly handled, in part at least, outside the specialty. In the handling of chronic neurological diseases, as well as those conditions other than chronic, that most usually present themselves in a neurologist's office, it has become increasingly necessary for the neurologist to have a proper orientation to psychiatry. There is little possibility of compensating for destroyed nervous tissue by any other than psychological methods.

As has been observed in these notes on recent advances, much of the newer neurological therapy is in the realm of psychotherapy. It ought to be superfluous in this area to note that psychotherapy is not made up of such banalities as the frequently recurring statement to the patient that there is nothing wrong with him or that he must pull himself together. It is now requisite that the neurologist as well as the practitioner have insight into human behavior,[6,12,19,25,27,34] if a large segment of their practice is not to be doomed to futility. As recorded by Halliday in his brilliant analysis, the trend to increased psychosomatic affections is very great and their nature cannot be understood nor can therapy be instituted in the absence of the application of psychosomatic and allied concepts.

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EDITORIALS

The Use of Vitamin Supplements

A great deal has been written in recent years regarding the failure of the diet of the average American to meet satisfactory nutritional requirements, in terms of the modern knowledge of nutrition. The war-time National Nutrition Program was based on the belief that many of us were subsisting on a diet inadequate for optimal nutrition and buoyant health. Without entering into a prolonged discussion of this problem, it seems worth while to point out the possible role of vitamin supplements in meeting this apparent deficiency. At present wheat flour, oleomargarine and certain cereals are being enriched with vitamins and minerals.

What of the widespread use of commercial vitamin preparations as supplements to the diet of Americans? Apparently this is a very widespread practice. Is it sound? There are two schools of thought on this matter. One group is of the opinion that many persons are benefited by so supplementing the diet, with the idea that if there is any possible chance that vitamins may produce better health, sounder teeth and bones, improve vision at night, increase appetites, decrease the incidence of infections, especially of the common cold, and decrease fatigue and increase energy, then the cost of the preparations and the nuisance of taking them would be worth while. If this conclusion were correct, of course all of us would agree with it. Most sound nutritionists and physicians hold the opinion opposite to the one just expressed and disapprove of the indiscriminate use of commercial vitamin supplements as unsound nutritionally and economically. Indeed, the opinion of this group as exemplified by the Council on Foods and Nutrition and by the Council on Industrial Health of the American Medical Association is that the giving of vitamin pills to presumably healthy adults working under normal conditions is irrational from the therapeutic point of view, unwise nutritionally, and uneconomical. The real solution to the problem is one of an adequate diet for every one, for vitamins are included and in such a diet they are in better balance, more palatable, and more economical.

Of what value then are vitamin mixtures? A committee of the American Medical Association after studying this problem came to the sensible conclusions that vitamin mixtures when properly formulated are convenient, economical and provide the physician rational means of treating or preventing multiple vitamin deficiency. It is wise in the formulation of acceptable mixtures that the vitamins in a product should be present in some simple relationship to the normal daily requirement of them. In so far as possible, natural products, such as cod liver oil and dried brewers' yeast, should be used in these mixtures to which may safely be added synthetic preparations such as thiamine, riboflavin, niacin, and ascorbic acid. These mixtures, so far as possible, should be used as supplements to a normal diet.

In the final analysis, benefit will be greatest when natural foods are least interfered with and when, in the preparation of his food, man makes few changes which need to be corrected subsequently by supplementing the diet with vitamin preparations.

The Coming 1947 Annual Meeting

The Annual Meeting of the California Medical Association will be held Wednesday, April 30 to Saturday, May 3, inclusive, at the Biltmore Hotel, Los Angeles. The following is a prelminary outline of the scientific program planned for this meeting:

There will be approximately ten large general meetings, the programs for which have been arranged by the cooperative efforts of the officers of several different sections. There will be approximately 25 special or section meetings in which from one to three sections have combined their talents in order to present a group of papers on modern scientific topics.

The guest speakers and their tentative subjects are as follows:

1. A. W. Oughterson, M.D., Medical Director of the American Cancer Society, New York City, will speak on "Planning the Attack on Cancer," "The Diagnostic Problem in Gastro-Intestinal Cancer," and one other subject. He will also discuss an important paper on Visible Tumor Clinics before the Section on Dermatology and Syphilology.

2. Hobart A. Reimann, M.D., Professor of Medicine, Jefferson Medical College, Philadelphia, will present papers on "Virus Pulmonary Diseases," "Periodic Diseases," and "What's New in Infectious Diseases." He will also conduct one of the cases in the Clinical-Pathological Conference.

3. James T. Priestley, Mayo Clinic, Rochester, Minnesota, will talk on "The Surgical and Physiological Aspects of the Treatment of Duodenal Ulcer," and will discuss one of the cases in the Clinical-Pathological Conference.

4. Albert Snell, M.D., Professor of Medicine, Mayo Foundation, Rochester, Minnesota, will talk on "The Management of Infectious Hepatitis," and "What's New in Gastroenterology," and will discuss certain other papers.

Preceding the meeting will be the annual Clinical Radiological and Pathological Conferences of the Cancer Commission. Proven cases of special diagnostic interest will be shown; improved therapeutic methods and end results will be discussed; miscellaneous histo-pathological tumor problems will be presented. These important sessions will be held on Tuesday, April 29, at a location to be announced in our next issue.

There is a trend toward the holding of more general meetings and fewer section meetings at annual state medical society conventions. You will be asked to express your opinion at the business meeting of your own section on the questions: "Do you wish more general meetings at annual sessions?" "Do you approve the holding of section meetings on one day of each annual session, with multiple brief papers, the others days to be devoted to general meetings?" Your Section Officers will also be asked to consider polling you on the question of appointing a Section Secretary for a period of about three years (instead of the current one year) so that the appointee may gain familiarity with the problems of arranging improved scientific programs and with other duties of the office.

If you plan to come to Los Angeles for the state meeting, it is suggested that you make your hotel reservations at once, and that you plan to stay for the full four days of the meetings. The opening session will be at 10 a.m. on Wednesday, April 30, and the closing postmortems on Saturday afternoon, May 3.

76th Annual Session
California Medical Association
Los Angeles
April 30—May 3, 1947

For hotel reservations, write Convention Department, Los Angeles Chamber of Commerce, 1151 South Broadway, Los Angeles, Calif.

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NOTICES AND REPORTS

NEWS *of the* DAY *in the* C. M. A.

January 5—Executive Committee and Committee on Public Policy and Legislation (Murray, Remmen, Kindall) meet to discuss legislative program. Session lasts to 5:30, by which time all are agreed that it is fortunate that legislative sessions come only once in two years. C.M.A. bills well mulled over.

January 11—Committee on Scientific Work in all-day meet with secretaries of scientific sections, arranging 1947 Annual Session program. Much progress made and an excellent program shaping up. Plan to print complete program in March issue CALIFORNIA MEDICINE and to have session programs available before meeting starts.

January 12—Council meets. This is the day when the small printed agenda stretches out to point where it is unanimously decided to make next Council meeting a two-day affair. Time conserved at lunch hour by serving buffet lunch. (There is still a discussion on whether you eat more at a table than when you serve yourself.) By end of day Council has digested seven verticle inches of file folders and still has unfinished business to turn over to Executive Committee. The next meeting will again be at the Fairmont on Saturday, March 15, through 16th.

January 16—An inquiry today as to the ability of a California clinic to diagnose and treat Parkinson's syndrome by mail. Inquiry and reply add to a fat file on a colleague (not Dr. Brinkley) who believes this can be done.

January 17—Meeting of C.M.A. Cancer Commission in San Francisco at 6:30 p.m. Items were discussed along the lines of a statewide project to help needy patients secure hospitalization when in hospitals for curative procedures; discussion of uniform records for Cancer Detection Centers and Tumor Boards; question of establishing central Tumor Registry either under C.M.A. control or Department of Public Health control; completion of details for publication of new edition of Cancer Commission Studies, the up-to-date informative booklet for doctors on what's new in cancer diagnosis and treatment.

January 20—California Committee for Voluntary Health Insurance opens drive in Sacramento County with meeting of civic and state leaders in Senator Hotel. Audience of 400 applauds John Cline in hard-hitting speech pointing out lack of need of regimentation to make medical service span the gap between doctor and patient.

January 22—Executive Committee eats at 6:30, meets at 7:30, goes home at 1:30 a.m. Problems of legislation and general business thrashed out until next meeting two weeks off.

January 23-24—Details of 1947 Annual Session worked out. House of Delegates will meet April 30 and May 2, general sessions on April 30 and May 2, specialty sections meeting May 1 to 3. Lively program promised. (For room reservations, write Convention Department, Los Angeles Chamber of Commerce, 1151 South Broadway, Los Angeles. Delegates write to C.M.A. office.)

January 28—Governor Warren takes the lid off his Pandora's Box and gives us just a peek at his 1947 model health insurance program. The initial look makes the whole affair look like Pandora, all right—there seems to be plenty of bugs.

January 30—Arrangements made for lunch on February 12—Lincoln Day—in honor of Doctor Walter Judd of Minnesota, one of the seven physician members of Congress. In California on a trip sponsored by the GOP, Doctor Judd will meet with medical leaders to discuss, among other things, medical legislation and health insurance.

January 31—Planning today for a joint legislative meeting with the dentists, pharmacists, dispensing opticians and allied groups. Started five years ago, these joint meetings bring out the strong and weak points in the several legislative programs, offer encouragement for beneficial bills and indicated treatment for others.

CPS—more members, income, problems, experience

Having surpassed all anticipated enrollment figures during 1946, California Physicians' Service has entered the new year well on the way to perfecting a prepay medical service program that will be a credit to the medical profession of California.

A glance at the record of achievement in 1946 shows:

In January, 1946, total beneficiary membership of California Physicians' Service was 176,880 people. As of January, 1947, slightly more than 420,000 Californians are participating in the C.P.S. commercial program. Nearly 250,000 new members were enrolled during the year, a rate of over 20,000 persons each month.

This enrollment is noteworthy because throughout the year employment turnover was at an all time high and the uncertainty of postwar conversion with its economic instability made the work of sales and reservice difficult. While business in general was undergoing its reconversion from war to peace, the California Physicians' Service membership rosters were constantly in flux. However, the C.P.S. sales and operational staffs proved that private organization methods can accomplish the tasks thus imposed.

When membership figures jumped in such a short period,

internal operational problems multiplied rapidly. Shortages of trained personnel and office equipment, combined with severe shortage of space, made the administration doubly complicated.

Again referring to the record, January, 1946, showed a monthly income of $253,000, as compared with $560,000 for January, 1947. It should be noted that these figures do not include the income derived from the Veterans' Administration-C.P.S. contract.

In the beginning of 1946, C.P.S. had 5,739 physician members. A year later the roster listed a participating physician membership of 7,781—a net gain of 2,042 new physician members during the year.

Besides the long strides made in the commercial program, the year saw establishment of the Veterans' service program and the farm program with the California State Grange. Under these, some 40,000 veterans have already been treated by private physicians (at government expense) and over 11,000 rural dwellers are participating in the new Grange program.

In Memoriam

COOKE, A. BENNETT. Died at Los Angeles, December 8, 1946, age 79. Graduate of Vanderbilt University School of Medicine, Nashville, Tennessee, 1891. Licensed in California in 1912. Doctor Cooke was a member of the Los Angeles County Medical Association; a Life Member of the California Medical Association since 1942, and an Affiliate Fellow of the American Medical Association.

✤

CRANE, HOMER WINFIELD. Died of a heart attack at Berkeley, December 19, 1946, age 66. Graduate of the Cooper Medical College, San Francisco, 1909. Licensed in California in 1909. Doctor Crane was a member of the Alameda County Medical Association, the California Medical Association, and a Fellow of the American Medical Association.

✤

HILL, HAROLD PHILLIPS. Died at San Francisco, December 31, 1946, age 70. Graduate of the University of California Medical School, 1901. Licensed in California in 1901. Doctor Hill was a member of the San Francisco County Medical Society, the California Medical Association, and a Fellow of the American Medical Association.

✤

HIRSHFELD, SAMUEL. Died from a coronary ailment, December 13, 1946, age 51. Graduate of Columbia University College of Physicians and Surgeons, New York, 1918. Licensed in California in 1932. Doctor Hirshfeld was a member of the Los Angeles County Medical Association, the California Medical Association, and a Fellow of the American Medical Association.

✤

SCHILLING, WALTER. Died at San Francisco, December 16, 1946, age 54. Graduate of Harvard Medical School, Boston, Massachusetts, 1925. Licensed in California in 1925. Doctor Schilling was a member of the San Francisco County Medical Society, the California Medical Association, and a Fellow of the American Medical Association.

✤

WESTERHOUT, CHARLES EDWARD. Died from myelogenous leukemia, at Oakland, November 20, 1946, age 44. Graduate of Stanford University School of Medicine, 1929. Licensed in California in 1931. Doctor Westerhout was a member of the Orange County Medical Association, the California Medical Association, and a Fellow of the American Medical Association.

Annual Drive of the American Cancer Society

The American Cancer Society has held an annual drive every year since 1914. Since that date, and especially since 1936 (when the Field Army of the Society was created), progressive groups throughout the country have supported the annual drive and program of the Cancer Society.

Since 1938, April has been designated by Presidential proclamation as National Cancer Control Month. The California Division of the American Cancer Society, under the vigorous leadership of Mrs. Ryer Nixon, State Commander, is completing preparations for its annual campaign to commence April 1, 1947.

THE PROGRAM

The twelve-point program of the California Division should be familiar to all physicians. The following shows how the funds collected in each annual cancer campaign are distributed:

I. *60% of our funds are distributed for cancer control in California.*

These funds are distributed in line with the following 12-point program adopted by the Board of Directors of the California Division of the American Cancer Society:

1. Financial support of established *tumor centers.*
2. Assistance in the organization of new *tumor centers* and financial aid in the provision of some equipment, apparatus and personnel.
3. Financial assistance to *detection centers* conforming to standards set by the California Medical Association and approved by it.
4. Financial support for the hospitalization of needy cancer patients.
5. Provision of surgical dressings and transportation for cancer patients.
6. Financial assistance for establishment of social service and visiting nurse service for cancer patients.
7. Allocation of funds for special clinical tests for the detection and diagnosis of certain types of early cancer at laboratory centers in Los Angeles and San Francisco.
8. Establishment of cancer information and educational centers throughout the state.
9. Organization of postgraduate courses for physicians in the diagnosis and treatment of cancer. (These courses are held in Los Angeles, San Francisco and other centers.)
10. Education of the public through radio, press releases, by qualified speakers and through the distribution of literature which presents the facts about cancer, its danger signals and proper treatment.
11. Promotion of legislation to provide better care for cancer patients.
12. Administration including campaign expenses.

II. *40% is expended by the National Office of American Cancer Society.*

1. 15% is applied to nation-wide education and administration.
2. 25% is devoted to all-out coordinated research in the nature, causes and cure of cancer directed by the National Research Council. (Some of these funds return to California for research.)

CALIFORNIA CANCER CONTROL PROGRAM

The chart below shows the component activities of the Cancer Society, the Cancer Commission and affiliated groups.

California Division, American Cancer Society

Lay Education; Service to Cancer Patients; Campaign for Funds

1. Financial support for the clinic program of the California Medical Association.
2. Financial support for post-graduate cancer courses for physicians.
3. Public education through meetings and distribution of literature.
4. Establishment of information centers.
5. Education through secondary schools and colleges.
6. Subsidies to tumor and detection centers.
7. Volunteer workers for tumor centers.
8. Hospitalization for needy cancer patients.
9. Home nursing and surgical supplies.
10. Social service and follow-up workers.
11. Hospital beds for advanced cancer patients.
12. Campaign for funds.

California Medical Association, Cancer Commission

Professional Education and Relation of Physicians to the Program

1. Supervision of lay education and medical service programs of the American Cancer Society.
2. Postgraduate cancer courses for physicians (cooperating with medical schools).
3. Medical Society meetings.
4. Symposia and cancer days.
5. Cancer manual for physicians.
6. Assistance in organization of detection centers.
7. Assistance in organization of new consultation tumor centers.
8. Survey of standards of tumor centers and detection centers on state level.
9. Cooperation with Cancer Committees of County Medical Societies.
10. Survey of cancer facilities and cancer needs with County Medical Society.
11. Central Tumor Registry with Department of Public Health.

California State Department of Public Health

Survey and Statistics; Education of Nurses and Medical Social Workers

1. Training of public health nurses, statisticians and medical social workers.
2. Statistical research.
3. Consultation for hospitals and clinics on record systems.
4. Assistance to local health agencies in developing cancer programs, e.g., public health nursing services.
5. Liaison with other governmental agencies — State and Federal.
6. Survey of cancer facilities in the state with Cancer Commission of C.M.A.
7. Central Tumor Registry (tentative).

Cancer Committee, County Medical Societies

1. Medical education in the County Society.
2. County Medical Society panels of physicians who will accept referred cancer patients for diagnosis and treatment.
3. Service on boards of directors and executive committees of County Branches of American Cancer Society.
4. Speakers' Bureau for lay education.
5. Approval of service projects of the American Cancer Society.
6. Stimulate the formation of tumor and detection centers where facilities are available.
7. Enlist physicians for Detection Centers.
8. Encourage use of Tumor Centers.
9. Assist in the April campaign for education and funds.

Council Meeting Minutes

TENTATIVE DRAFT OF THE MINUTES OF THE 338TH MEETING OF THE COUNCIL, CALIFORNIA MEDICAL ASSOCIATION

The meeting was called to order by Chairman Bruck at 9:30 a.m., Sunday, January 12, 1947, at the Fairmont Hotel, San Francisco.

1. *Roll Call:*

Present were President-Elect Cline, Speaker Askey, Vice-Speaker Alesen, Councilors Johnston, Crane, Henderson, Anderson, Kneeshaw, Bruck, Kindall, MacDonald, Green, Cherry, MacLean, Shipman, Moody, Thompson and Regan, Secretary Garland, and Editor Wilbur.

Absent: President McClendon (grounded by bad weather enroute to meeting).

Present by invitation were: Dwight H. Murray, Chairman of Public Policy and Legislation; Philip K. Gilman of the State Department of Public Health; Messrs. Howard Hassard and George Smith of legal counsel; executive secretaries Frank Kihm and Rollen Waterson of San Francisco and Alameda counties; Mr. Clem Whitaker, public relations counsel; Mr. Ben Read, legislative representative; Mr. William Bowman, executive director of C.P.S.; Mr. Jay Ketchum, executive vice-president of Michigan Medical Service; Mr. John Hunton, executive secretary, and Mr. William Wheeler, assistant executive secretary.

2. *Minutes:*

On motion duly made and seconded, the minutes of the 337th meeting of the Council were approved with the following corrections:

(a) Item No. 9 to show that the outline presented informally by Doctor Russel V. A. Lee to President-Elect Cline constituted a tentative proposal only and not an abstract of Dr. Lee's report to the Senate Interim Committee on Health Insurance.

(b) Item 6(a) to show the additional appointments of Doctors George Uhl and William P. Shepard as members of the Editorial Board, representing public health.

(c) Item 14 to show the presentation of a request for legal opinion from Alameda County regarding funds received for medical services from part-pay patients in county hospitals. This request was referred to legal counsel for opinion.

3. *Membership:*

(a) A report of membership as of January 10, 1947, was received.

(b) On motion duly made and seconded, 11 members whose 1946 dues had been received since November 10, 1946, were reinstated to active membership.

(c) On motion duly made and seconded, it was voted that the central office send notification to all county societies regarding the so-called election of regular members to county societies who are not members of the Association and pointing out the constitutional prohibition against such elections. Members must pay county and state dues to be a member of the county society.

(d) On motion duly made and seconded, seven members were elected to Retired Membership. These were: Clark J. Burnham, Sr., Alameda County; Marie H. Heinatz, Alameda County; Martin J. Lacey, Alameda County; Benjamin Thomas, Alameda County; Robert A. Campbell, Los Angeles County; C. Zeno Holt, Alameda County, and Grunyd C. Coffey, Ventura County.

(e) On motion duly made and seconded, three members were elected to Associate Membership. They were as follows: David Frost, Alameda County; Loren Larsen, Alameda County, and William S. Fife, San Joaquin County.

(f) The situation in San Francisco County, where certain members, including Doctors Ernst Wolff and Leona Bayer, have had their membership terminated because of delinquent payment of a portion or all of their 1946 dues, was discussed. Doctors Wolff and Bayer have applied to the C.M.A. for a review of their cases. Mr. Hassard pointed out that the Council should set a date for the hearing of their appeals and appoint a committee to try to effect a reconciliation of the differences. On motion by Cline, seconded by Alesen, it was voted that the date of the next Council meeting be set as the date of the hearing and that Doctors H. Gordon MacLean, Lloyd Kindall, and R. S. Kneeshaw be named as the conciliation committee.

4. *Financial:*

(a) A statement of cash balances as of January 10, 1947, a statement of income and expenditures for December and for the six months ended December 31, 1946, and a balance sheet as of December 31, 1946, were received.

(b) On motion by Green, seconded by Moody, it was voted to transfer to the Trustees of the California Medical Association the $150,000 in U. S. Treasury bonds purchased as authorized at the 337th Council meeting.

(c) Doctor Cline reported on conferences held in regard to the salary of the Editor. He moved, seconded by Anderson, that the Editor's salary be set at $300 per month, retroactive to the time the Editor took office, early in May, 1946.

Doctor Alesen offered an amendment, which was seconded, to set the Editor's salary at $500 monthly. The amendment was lost on a vote of 2 ayes and 7 noes.

The original motion was then unanimously voted.

5. *Public Relations:*

(a) Mr. Whitaker reported on the present state of the public relations campaign, particularly with reference to the new proposal for a compulsory health insurance bill by Governor Warren. He stated his belief that the Association is better prepared to meet this legislative threat than it was two years ago, principally because of the continued program of public education in support of the voluntary forms of health insurance available to the people of California.

(b) Mr. Hunton discussed the advertising program in the Alameda County Medical Association, which has established a Bureau of Medical Economics to handle, among other things, the collection of past due accounts and the establishment of fair medical fees in proportion to the ability of the patient to pay. Through the operation of this program, the county medical society believes it is able to guarantee that all residents of Alameda County may secure needed medical attention at a cost within their means.

An advertisement to this effect was run in the daily newspapers of Alameda County in late December, 1946, at which time an open letter was sent to Governor Warren, notifying him that the

Alameda County Medical Society had tried to locate that person who needed medical attention and had not received it because of his belief that he was unable to pay its cost.

Mr. Hunton stated that at a joint informal meeting of the Executive Committee and the Committee on Public Policy and Legislation held on January 5, 1947, a resolution had been adopted to petition the Council for a continuation of this campaign and possible campaigns in other counties, the C.M.A. to furnish financial and other assistance.

There was general discussion on the possibilities of public education through such a campaign and on the cost of such advertising.

An amendment was offered by Kindall, seconded by MacLean, that copies of such advertisements be sent, at the discretion of the Committee on Public Policy and Legislation and the public relations counsel, to all members of the State Legislature and to the secretaries of all county medical societies. This amendment was unanimously adopted.

A further amendment was offered by Askey, seconded by Moody, that the cost of such advertising to the Association be limited to not more than $10,000. This amendment was unanimously adopted.

The original resolution, as amended, was then put to a vote and adopted.

6. *Public Policy and Legislation:*

Doctor Murray reported on a meeting held between members of the Executive Committee and the Committee on Public Policy and Legislation.

Mr. Read reported on the status of the Legislature and discussed the information available in Sacramento.

Mr. Hassard was then called upon to discuss individual bills which had been ordered introduced by the House of Delegates or otherwise agreed upon at previous meetings. Among these were bills:

(1) To provide that an employer may contract for the cost of voluntary health care for all his employees except those who request to be omitted from such coverage.

(2) To insure the right of an individual to dispose of all or any part of his body at death.

(3) To insure that relatives of a deceased person carry out the expressed wishes of the deceased as to the disposal of all or any part of his body.

These measures were ordered by the 1946 House of Delegates and bills prepared for introduction at this session of the Legislature.

(4) On the House of Delegates order to introduce legislation to replace the coroner system with a system of medical examiners, Mr. Hassard called attention to the practical difficulties of drafting such legislation, particularly since every reference to the coroner in every code on the statute books would require amendment. He stated that the author of the original House of Delegates resolution had been apprised of these difficulties and had suggested that a resolution be introduced to establish an interim committee of the Legislature to study the coroner system with a view toward improving it, including an investigation of the medical examiner system.

On motion by Cline, seconded by Alesen, it was unanimously voted that the Council express its opinion that there is a grave question concerning the wisdom of introducing the proposed House of Delegates legislation at this time, that the Council express complete confidence in the Committee on Public Policy and Legislation and wishes to support this committee before the House of Delegates should the question arise that the committee had not been able to comply fully with the wishes of that House.

(5) Hospital District Law — Mr. Hassard reported the agreement of Legislative and Executive Committees on a bill to provide that hospitals constructed under this law operate under the minimum standards of the American College of Surgeons and/or the Council on Medical Education and Hospitals of the A.M.A., and be prohibited from employing physicians in such a manner as to bring a financial profit to the hospital.

On motion by Cline, seconded by Askey, this bill was unanimously approved.

(6) Sickness disability law — two amendments to this bill have been proposed, one to eliminate chiropractors as recognized "physicians" within the meaning of the law, and (2) restrict to a statement of physical findings the certificate signed by the physician in cases coming under this law.

On motion by Cline, seconded by MacDonald, it was unanimously voted that the Legislative Committee introduce these amendments.

(7) Medical Practice Act—The removal of licensing requirements from first-year residents (in addition to internes) in approved hospitals was discussed. It was suggested that hospitals approved for resident training should not be penalized in the securing of first-year residents by the requirement that such residents first obtain California licenses.

On motion by Cline, seconded by Moody, it was unanimously voted that the Legislative Committee be authorized to introduce a bill to add the words "and residents" to the present law which permits the service of "internes" without licenses in approved hospitals for a period of two years.

(8) S.B. 1306 of the 1945 session—This bill was introduced for Hospital Service of California, to provide that insurance companies organized under the non-profit sections (Blue Cross sections) of the Insurance Code be allowed to indemnify their policyholders for surgical procedures performed outside of hospitals. The C.M.A. opposed this measure in 1945 and it was not passed. Doctor MacLean stated that H.S.C. now wished to re-introduce a similar measure.

It was moved by Kneeshaw and seconded by Anderson that the Association disapprove proposed reintroduction of this bill. An amendment by Shipman, accepted by the mover and second, added that the disapproval was based upon the reason that such a bill would set back the efforts of both medical and hospital interests to effect a consolidation of effort of existing medical service and hospitalization interests. On a vote, the amended motion was carried unanimously except for Councilor MacLean, whose vote was recorded as "no."

(9) Doctor Philip K. Gilman discussed the present problems of rural medical care and urged that a committee of two or three Councilors be appointed to meet with the Director of Public Health and others to work on such problems. On motion by Kneeshaw, seconded by Moody, it was voted that a committee of three be so appointed.

Doctor Gilman also urged that the Association participate in the prospective work of a Committee on Hospital Care proposed to include representatives of medicine, dentistry, nursing, hospitals, the State Department of Health, etc. No action was requested on this matter.

(10) Funds of county hospitals—Discussion was held on the advisability of introducing or supporting a bill to provide that funds received by county hospitals from part-pay or full-pay private patients, representing payment for professional medical services rendered by members of county medical societies, be turned over to such county medical societies for professional scientific purposes. On motion by Cherry, seconded by Green, it was voted that the Legislative Committee confer with representatives of the Association of California to determine whether or not that association would be agreeable to supporting such legislation and, if so, would be willing to introduce it.

(11) Average daily school attendance—A letter asking the signified approval of the Association on a petition to amend the school laws by permitting absences due to illness to be counted as school attendance in calculating state funds paid to school districts on an average daily attendance basis was presented. On motion by Kindall, seconded by Kneeshaw, it was voted that the Council signify such approval.

(12) State Board of Health Legislative Program—Mr. Hassard was called upon to discuss various legislative proposals of the State Board of Health. These were as follows:

(a) Additional aid for tuberculous patients. Approved by Council.

(b) Additional state aid to local health departments—not approved.

(c) Increasing hospital districts to maximum county population of 500,000 from present 200,000. Not approved.

(d) Blood banks—State Department of Health to offer technical assistance and supervision to community blood banks for procurement of blood for processing by private laboratories. Approved by Council.

(e) Funds for State Department of Health to carry on research in heart disease, cancer and chronic conditions. Not approved.

(f) Hospital subsidies—to provide state funds to furnish half of amount to be raised within the state to match on a 2-to-1 basis the federal funds available under the Hill-Burton bill. It was brought out that such funds would be available only to county hospitals unless a state constitutional amendment is passed by the Legislature and later by the people. On motion by Cline, seconded by Kneeshaw, the Council approved this measure and further provided that the Legislative Committee be authorized to prepare a bill for a hospital loan law suitable for use by municipal and private hospitals.

(g) Hospital survey act—to provide for the State Department of Health to receive federal funds for hospital construction. Approved by Council.

(h) Crippled Children's Act—to eliminate court approval and procedure in crippled children's cases and to substitute therefor the approval of the State Department of Health and State Department of Social Welfare. Not approved.

On motion by Cline, seconded by MacDonald, it was unanimously voted to authorize the Committee on Public Policy and Legislation to modify all instructions on positive actions given by the Council, in accordance with exigencies arising during the course of the legislative session.

7. *California Physicians' Service:*

Mr. Bowman reported that January revenues of C.P.S. amounted to an annual rate of $9,180,000, divided $6,180,000 for commercial program and $3,000,000 for the veterans' program. The deficit at the start of January was $197,042, or the equivalent of only 11.7 days of income.

Utilization of service has increased from an average of $18 a case to about $23 a case, much of this utilization representing a high demand for elective surgery. There are now 7,690 physician members, many of them returned veterans who have enjoyed practically unlimited laboratory services in military life and carry this program into their private and C.P.S. practice. A slight reduction in the average cost per case is now appearing.

The increase of 25 per cent in members' dues has now been applied to about 70,000 members and is being applied as rapidly as group contracts expire and come up for renewal. The total commercial membership in January, 1947, was 419,000, an increase of 137 per cent over the 177,680 members a year earlier. There are now 122,000 members served with hospitalization in northern California. At the present rate of growth C.P.S. expects 1,000,000 members by January, 1949. The growth in membership is attributed in large part to the public relations program of the C.M.A. The community enrollment drives in the C.M.A. programs are considered successful on the whole, although there have been some instances where results are not entirely satisfactory.

Mr. Bowman reported further on the business survey of C.P.S. made by McKinsie & Co., business analysts, in response to one of the recommendations of the C.M.A. Committee on Prepaid Medical Care. This survey shows that the difficulties experienced by C.P.S. are mainly the results of growing pains, including inadequate office space and inadequate and untrained personnel. The survey indicates that the business policies and practices of C.P.S. are in accord with sound business standards but must be altered as further growth takes place and makes inadequate those systems and methods which are ample to handle today's business. C.P.S. plans to make this type of business survey a continuing check on its organization.

8. *Congress of Parent-Teachers Association:*

Chairman Bruck announced the appointment of E. Vincent Askey as chairman of a committee to meet with a similar committee from the P-T A to discuss problems of mutual concern. Doctors Louis J. Regan and H. Gordon MacLean will also serve on this committee. It was agreed

that the Association notify all county society secretaries to contact their local P-T A organizations and work with them on the program of pre-school physical examinations.

9. *University of California at Los Angeles Medical School:*

A report was made that a dean had been tentatively selected for the medical school to be formed at the University of California at Los Angeles but that his appointment had been temporarily put over. On motion by Alesen, seconded by Moody, it was unanimously voted that the Council offer every assistance to the Board of Regents of the University of California in the selection of a dean for the UCLA medical school and that the Council chairman notify the chairman of the Board, Dr. Robert Gordon Sproul, to that effect.

10. *Board of Nurse Examiners:*

Doctor Cline reported on the issuance of an order by the Board of Nurse Examiners limiting the attendance of student nurses in classes or in clinical work to a maximum of 40 hours per week. This order is being protested by at least two schools of nursing (Standard and UC) and by the Association of California Hospitals. On motion by Cline, seconded by Kneeshaw, it was voted that a committee be appointed to meet with the Association of California Hospitals to work out a suitable program to combat this order.

11. *Cancer Commission:*

The Secretary presented a resolution adopted unanimously by the Cancer Commission at its meeting on December 28, 1946, and transmitted to the Council for its information. He explained that the essential reason for the adoption of the resolution was the need for clarification in regard to the drive for funds by the official statewide organization responsible for the State Cancer Program. The preamble of the resolution listed 16 important points concerned with the over-all statewide cancer picture in California; the resolution itself was as follows:

RESOLVED, By the Cancer Commission of California Medical Association that this Commission do, and it hereby does, by unanimous vote, recommend to the Board of Trustees of Cancer Prevention Society that it postpone until May 1, 1947, the continuance of its campaign for funds. Further that if this be not done, we respectfully recommend that the Los Angeles County Medical Association as a constituent member of California Medical Association, withdraw the approval which it has heretofore given to the Cancer Prevention Society, for the reason that, as stated in the preamble, cancer control in California on a statewide level will be seriously jeopardized.

The Secretary explained that the Chairman of the Cancer Commission requested that the matter be brought to the attention of the Council and that he respectfully requested the Council merely to take it under advisement at the present time.

12. *Palo Alto Clinic:*

The status of the Palo Alto Clinic contract with Stanford University was discussed and it was brought out that the Executive Committee was due to make a report on this matter. On motion by Cline, seconded by Moody, it was voted that the report be considered at the next Council meeting and that the parties at interest be invited to be present at that time.

13. *Time and Place of Next Council Meeting:*

It was voted to hold the next Council meeting at 12:30 p.m. lunch on Saturday, March 15, 1947, to continue that afternoon and the next day, Sunday, March 16, at the Fairmont Hotel, San Francisco.

Adjournment.

76th Annual Session
California Medical Association
Los Angeles
April 30—May 3, 1947

For hotel reservations, write Convention Department, Los Angeles Chamber of Commerce, 1151 South Broadway, Los Angeles, Calif.

NEWS and NOTES

NATIONAL • STATE • COUNTY

ALAMEDA

Berkeley Hospital has been renamed **Herrick Memorial Hospital** in honor of LeRoy Francis Herrick, M.D., who founded it in 1904.

FRESNO

Dr. Edwin A. Patterson, Fresno physician and surgeon, has been installed as president of the **Fresno County Medical Association.** He succeeds Dr. Jerome A. Thormann. Other new officers include Dr. Kenneth Leuchauer, first vice president; Dr. William L. Adams, Jr., second vice president; Dr. William Knudsen, secretary-treasurer; Dr. Dwight Trowbridge, librarian.

LOS ANGELES

After three years' overseas service, **Dr. Saul Moss** has resumed his practice as physician and surgeon with new offices at 15200 Ventura Boulevard, Sherman Oaks.

Dr. John P. Nuttall of Santa Monica has been appointed city physician. A former member of the City Health Commission, Dr. Nuttall has taken an active part in medical association activities. He is a past officer of the medical legal committee of the Los Angeles County Medical Association and past president of the Santa Monica branch of the same organization.

Captain E. Crawford May has resigned as president of the Hastings Foundation, Pasadena, and has been succeeded by **Dr. LeRoy B. Sherry,** Pasadena surgeon, who was unanimously elected. Captain May will remain on the board. The Hastings Foundation owns and administers the Hastings Sanitorium, a tuberculosis research center in the Lincoln Avenue foothills.

Cedars of Lebanon Hospital has announced the appointment of **Dr. Trace Jackson Putnam** to its medical staff as chief of neurosurgery. A former professor at Harvard Medical School, Dr. Putnam has been working in neurology and neurological surgery at Columbia Medical and Neurological Institute, New York. He is editor-in-chief of "Archives of Neurology and Psychiatry."

The **Trudeau Society** of Los Angeles, which constitutes the Tuberculosis Section of the Los Angeles County Medical Association, has elected the following officers for the year 1947: President, **Edward Kupka, M.D.;** Vice President, **Joseph L. Robinson, M.D.;** Secretary-Treasurer, **Arthur E. T. Rogers, M.D.**

NAPA

Dr. Theodore K. Miller, medical director of the Napa State Hospital, has announced the addition of several doctors to the institution staff. They are Dr. Maleta Boatman, physician and surgeon from the Langley-Porter Clinic in San Francisco, Dr. Clara L. Hughes, physician and surgeon, and Dr. William Glosson, psychiatrist.

ORANGE

Dr. Russell I. Johnson of Midway City is the new president of the **Orange County Medical Association,** succeeding Dr. John J. Montanus, former head of Orange County Hospital. Other officers elected were: Dr. Milo Tedstrom of Santa Ana, vice president; Dr. L. E. Wilson of Anaheim, secretary-treasurer; Dr. C. C. Violett of Garden Grove, librarian; Dr. A. H. Wightman of Laguna Beach, councilor; Dr. L. F. Whitaker of Huntington Beach, bulletin editor; Dr. Edward Lee Russell of Santa Ana, associate editor.

RIVERSIDE

Members of the Riverside County Medical Association recently attended a meeting to hear a Symposium on "Choice of Surgical Suture and Early Ambulation" at the Community Hospital. Speakers at the meeting were **Dr. Cecil Lord,** who spoke on the absorbable suture; **Dr. Ray B. McCarty,** on the non-absorbable suture; **Dr. Omar W. Wheeler,** on non-absorbable suture wire, and **Dr. Franklin B. Mead** on early ambulation. The California Physicians' Service-Veterans' Administration program was also discussed by **Dr. W. H. Gardenier,** assistant medical director of C.P.S.

SAN DIEGO

Dr. Hugh Allen Frank, a former resident of El Cajon, who recently returned from military service, has become associated with Drs. Morten N. Carlile and George W. Morris at El Cajon. Dr. Frank is a graduate of the University of Chicago.

SAN FRANCISCO

San Francisco's first **curative workshop,** designed to lessen the gap ordinarily existing for disabled persons between the period of treatment and their return to work, is in operation at its new headquarters at 1680 Mission Street. The center is a non-profit organization wherein occupational and physical therapy are correlated with work tolerance and work adjustment programs. It is sponsored by the San Francisco unit of the American Women's Voluntary Services and among those serving on the board are **Dr. Frederick C. Bost** and **Dr. George Johnson,** both of San Francisco. In addition, the center has a medical advisory board which includes the city's leading orthopedists, internists, industrial surgeons, pediatricians, psychiatrist and plastic surgeons.

Appointment of **Dr. Norman Reider** as chief of the Psychiatric Clinic at Mount Zion Hospital in San Francisco has been announced by **Dr. Julius A. Katzive,** director of the hospital. Dr. Reider succeeds the late **Dr. J. S. Kasamin** who organized the clinic in 1939.

The importance of the proposed **Mount Zion Medical Center** was emphasized recently by Dr. Anthony B. Diepenbrock, president of the San Francisco

County Medical Society. It would provide facilities for many future physicians and surgeons who now are forced to go to educational institutions in other states to obtain their training, Dr. Diepenbrock said. The Mount Zion Hospital Appeal Committee recently reported that contributions to the $3,250,000 fund now total about $1,500,000.

Dr. Howard C. Naffziger of San Francisco has been elected to the regents of the American College of Surgeons for the 1947-48 term.

SAN MATEO

A committee of five has been named to formulate a program for the newly organized **Mental Hygiene Society of San Mateo County.** The committee consists of Dr. Logan Gray and Dr. Kenneth Rew of San Mateo, Miss Ruth Melendy, San Carlos school superintendent, Mrs. Kathryn Bell, county child welfare department, and Mrs. Ruth Bevilockaway of San Mateo.

Dr. Vernet H. Heinz has returned to practice at the 329 Primrose Road building, Burlingame, after serving with the Navy during the war.

SANTA CLARA

Two certified anesthetists have joined the permanent staff of the **Palo Alto Hospital.** They are Dr. John Stiles, associate professor of anesthesiology in the Stanford Medical School, and Dr. Malcolm Hawk.

More than 50 pathologists from all over the state met recently on the Stanford campus for the mid-winter **diagnostic conference** of the California Medical Association's **Cancer Commission.** The conference was designed to arouse interest in cancer and to sharpen the diagnostic skill of the pathologist, according to **Dr. David A. Wood** of the Stanford School of Medicine, commission secretary. Twenty difficult cancer cases were discussed.

SUTTER

Dr. Thomas F. Keyes has resigned as Sutter County Physician and has been replaced by Dr. Dudley Grant of Grass Valley.

TULARE

Dr. Frank Guido, Visalia physician and surgeon, was chosen president of the **Tulare County Medical Society** at the annual election meeting in Visalia. He succeeds Dr. George Keiper of Visalia. Other officers chosen were Dr. W. B. Parkinson, Porterville, vice president; and Dr. Debora Pineles, Visalia, secretary-treasurer.

YOLO

Dr. W. D. McCarthy of Oakland met recently with Yolo County directors and physicians to perfect plans for a spring **Cancer Control drive.** Last year more than $4,000 was raised for cancer control in Yolo County.

Dr. J. Homer Woolsey of Woodland has been elected to the board of governors of the American College of Surgeons for the 1947-48 term.

YUBA

Dr. William Vasquez has resigned as Yuba County physician. He plans to enter private practice in Marysville.

GENERAL NEWS

The activities of the **Psychiatric Personnel Placement Service** jointly operated for the past year as an emergency placement program by the American Psychiatric Association and The National Committee for Mental Hygiene, 1790 Broadway, New York 19, New York. Applications from physicians seeking placement in positions or in training in the field of psychiatry are still invited.

Over 900 physicians have registered with the Placement Service since it began operating on December 11, 1945, for the purpose of giving **advice and assistance** to physicians in the armed forces who were interested in obtaining further training or positions in psychiatry on their return to civilian life. It is felt, however, that the emergency placement program has been completed, but that the data relative to training and positions should be kept available to interested physicians. The complete file of **positions and training opportunities** in psychiatry, obtained by the Placement Service through nation-wide surveys of general and state hospitals, private mental hospitals, community and mental hygiene clinics, medical schools, and foundations, will be located in the offices of The National Committee for Mental Hygiene.

One hundred radiologists will be selected to attend the **postgraduate courses in radiology** to be conducted March 30 through April 4 in Philadelphia by the American College of Radiology. Preference will be given to radiologists who served in World War II. Second preference will be given to qualified applicants who were unable to obtain admission to last year's course in Philadelphia. The course is sponsored jointly by the American College of Radiology and the Philadelphia Roentgen Ray Society.

Although national and local scientific societies in the specialty of radiology have maintained a consistently high standard in their regular meetings, numerous inquiries have indicated an obvious need for intensive courses of a more academic nature. Also, **veteran medical officers** have been felt to be in need of an intensive review before returning to private practice. Many of these men were denied the opportunity for normal clinical practice or study which would keep them abreast of the rapid progress in the specialty of radiology.

Some of the **subjects to be studied** are: Certain neoplastic and inflammatory diseases, carcinoma of the head and neck, dosage calculation and tumor sensitivity in radiation therapy, carcinoma of the breast, blood and hemopoetic diseases, carcinoma of the genital and urinary tract, benign and malignant diseases of the skin.

A fellowship for the study of the application of newly developed radioactive isotopes to clinical medicine is offered for 1947 by Permanente Foundation. Announcement of the offer says that an attempt will be made to apply basic investigational study in biophysics to the care of clinic and hospital patients. **Appointments** will be awarded to graduates of Grade A medical schools who have completed an approved interneship. Research fellows receive $225 monthly, plus tuition costs and partial maintenance. **Applications** should be mailed to: Chairman, Fellowship Committee, Permanente Foundation Hospital, 280 MacArthur Boulevard, West, Oakland 11, California.

California Society for Crippled Children will hold its **Easter Seal sale** again this year. Returns from sale of Easter Seals last year showed a 26 per cent increase to $3,420,000, according to W. E. Griffith, executive director of the Society, but "needed services for crippled and spastic children far outrun this amount."

Need for full-time, **active-duty Navy medical officers** and for others for part-time duty with organized reserve units is announced by G. B. Ribble, Captain (MC), U.S.N., staff medical officer of the Naval Air Reserve Training Command. Opportunity for reserve officers to return to active status at **any of 16 major stations** or six training units is set forth in an advertisement by the Air Reserve Training Command. Duty would be in the Naval Air Reserve Training Program which has as its mission the maintenance of combat efficiency of previously trained naval aviators. Openings for active duty are announced at **Oakland,** California; Atlanta; Dallas; Glenview, Illinois; Grosse Ile, Michigan; Memphis; Minneapolis; New Orleans; Olathe, Kansas; Squantum, Mass.; St. Louis; Willow Grave, Pa.; Denver; Jacksonville; Miami; and **Seattle.**

Cooperation of doctors and other community leaders in local and national efforts to **stamp out venereal disease** is asked in a letter sent to physicians by Charles Walter Clarke, M.D., executive director of the American Social Hygiene Association.

Although scientifically America is closer to **victory** over VD than ever before in history, Dr. **Clarke** points out that the **VD rates are rising generally,** with the sharpest upturn in the youth group. "It is essential," he says, "that we strengthen protective and preventive measures if we hope to bring down VD rates." To this end, Dr. Clarke asks that physicians get behind a "broad program of community organization and public information" now going forward under the leadership of the American Social Hygiene Association.

INFORMATION

Suggested Program for Development of Blood Bank Services in California*

Blood and plasma banks have been proved essential for efficient, safe, and more economical transfusion services in the practice of medicine. The importance of whole blood over plasma is expressed by the demand for five units of blood to every unit of plasma in the hospitals which are now served by blood banks.

A Summary Concerning the Present Blood Banks in the State:

1. There are 28 blood banks in the state at present. Eleven are located north of a horizontal line through Fresno, and 17 are in the southern part of the state. (See Map I.)

2. Blood banks are divided into three groups: 5 community type banks; 9 county hospital banks; and 14 hospital or private banks.

3. Eighty-four hospitals containing 17,559 beds receive blood and plasma from these banks. This represents less than one-half the general hospital beds in the state, and therefore less than 50 per cent of all general hospital beds are now being served by blood banks.

4. In response to a questionnaire 64 per cent of the hospitals which are without blood bank services said they were in favor of a state-wide program, 26 per cent were undecided, and 10 per cent were not in favor of such a program.

5. In 1945 the 84 general hospitals used about 61,000 units of whole blood or an average of 3.5 units per general hospital bed per year. They also reported having used approximately 7,500 units of plasma. The total needs of the state are estimated to be approximately 140,000 units of whole blood per year on the basis of four units per bed per year, and approximately 28,000 units of plasma per year.

6. A questionnaire to the hospitals which do not share these bank facilities disclosed that the average use of blood is less than one unit per bed per year.

7. Under the spontaneous development of the blood banks in the state the community type of blood bank has been formed in only a few areas. The lack of community blood banks has resulted in an uneven distribution of blood. Northern California with a potential 32 per cent of the population now receives 65 per cent of the total blood from the banks, and Southern California with 48 per cent of the population which might be served has only 35 per cent of the total bank blood. There are three areas without any available banks.

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* Excerpts from a report submitted by the State Department of Public Health to the Governor and to the Fifty-seventh Session of the California Legislature Pursuant to Senate Concurrent Resolution No. 57 passed by the 56th Session.

8. At present four of the five community banks are located in the San Francisco Bay area. These four banks serve almost all the hospitals in the area, and they furnish almost as much blood as the remaining 24 banks which are currently operating in the state. (See Table 1.)

9. The standards to which the banks adhere are quite variable. Many practices now carried on are questionable, if not potentially dangerous.

10. The locations, size, and physical equipment of many banks make expansion of their present facilities an impossibility.

MAP I

LOCATION OF 28 BLOOD BANKS IN CALIFORNIA IN 1946

Recommendations for the Solution of the Problem:

1. It is recommended that the state be divided into 14 separate blood bank areas approximately as outlined in Map II.

2. It is recommended that there be a local community blood bank in each of these 14 areas.

3. It is recommended that these blood banks be financed and maintained by local funds. The procedure for current financing may vary from bank to bank but experience has shown that the payment of a processing charge by the patient receiving the blood is a feasible method for maintaining the blood bank. Such charges vary from $5 to $10 per unit of blood, depending upon the volume of units handled. Another possible procedure is for the community to finance the bank from donated and/or public funds. The administration and the distribution of blood should be a local function under locally employed personnel. Local, civic and public agencies should cooperate in establishing and maintaining each bank.

4. It is recommended that the State Department of Public Health provide personnel to assist in the establishment of the community blood banks; to integrate the activities of the community blood banks; to serve as consultants and to require the maintenance of high standards in all blood banks in California. In the initial phase of the program such personnel will be one physician, one blood bank technician, and one expert in community organization and public health education.

5. It is recommended that the State Department of Public Health assist financially to the extent of not more than 50 per cent or a maximum limit of $10,000, whichever is less, in the cost of establishing any community blood bank, or in covering the cost of needed expansion of facilities of any existing community bank during any one year.

6. It is recommended that blood fractions be processed, if possible, by commercial biological laboratories under a contract with the State Department of Public Health, or by the State Department of Public Health, and returned for distribution.

7. It is recommended that the California Medical Association, the Association of California Hospitals, the Association of Osteopathic Physicians and Surgeons, the American Red Cross, and other interested state-wide agencies assist the State Department of Public Health in the furtherance of these plans through their constituent state and local organizations.

8. It is recommended that an advisary committee be appointed by the State Board of Public Health to advise in the administration of the program. Such an advisory committee should be composed of representatives from blood banks, physicians and hospital organizations, and other groups which may aid in the development, maintenance and coordination of the program.

9. It is recommended that an appropriation of $75,000 be made to perform the above tasks during the first year.

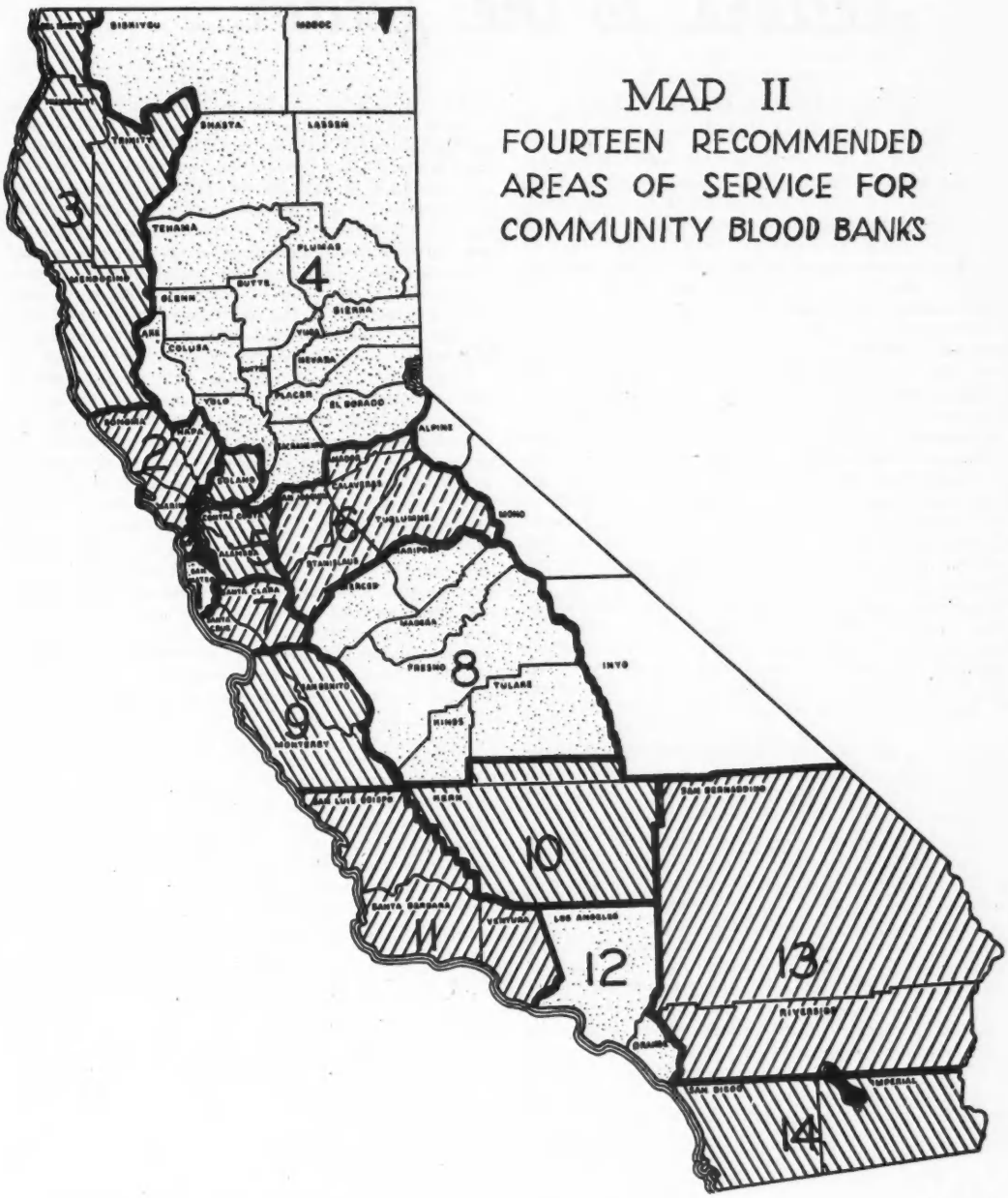
10. As the state-wide blood bank program develops, it may be necessary for the Department of Public Health to participate in the financing of the processing costs for plasma and blood fractions. The details of this part of the program remain to be formulated. Present indications are that the Red Cross surplus of these products will be ample for the next 18 months to two years, and consequently no recommendations on this point can be made at this time.

TABLE 1.—*General Summary of Blood Banks in California*

Type of Bank	No. of Banks	No. of Blood Units Used	No. Banks Making Plasma	No. of Plasma Units Used[2]	Replacement Requirement
Community	5	33,562[1] 28,762	4	3,700	3 (1:1) 2 (0:1)
County hospital	9	14,557	6	2,839	3 (1:1) 6 (2:1)
Laboratory or Hospital	14	13,126	2	972	9 (1:1) 5 (2:1)
Total	28	61,245	12	7,511	15 (1:1) 11 (2:1) 2 (0:1)

Type of Bank	Median Cost Per Unit	No. of Hospitals Cooperating[4]	No. of Beds Supplied[3]	Units of Blood per Bed[3]	Units of Plasma per Bed[3]
Community	$ 7.50	54	6,723	4.9[1] 4.2	.55
County hospital	0	9	6,518	2.2	.44
Laboratory or Hospital	$15.00	21	3,060	4.3	.32
Total	$ 7.50	84		3.8	.46

1 Based on 1945 reports, Red Cross (1946 estimates) included.
2 Estimated usage included, but not Red Cross or commercial plasma.
3 Does not include tuberculosis beds.
4 1946 data.


MAP II
FOURTEEN RECOMMENDED
AREAS OF SERVICE FOR
COMMUNITY BLOOD BANKS
SISKIYOU
MODOC
SHASTA
LASSEN
TRINITY
TEHAMA
PLUMAS
BUTTE
GLENN
SIERRA
COLUSA
NEVADA
PLACER
EL DORADO
YOLO
ALPINE
NAPA
CALAVERAS
TUOLUMNE
MONO
MARIPOSA
STANISLAUS
SANTA CLARA
MADERA
FRESNO
INYO
TULARE
SAN BENITO
KINGS
MONTEREY
SAN LUIS OBISPO
KERN
SAN BERNARDINO
SANTA BARBARA
VENTURA
LOS ANGELES
RIVERSIDE
ORANGE
SAN DIEGO
IMPERIAL
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Letters to the Editor . . .

RECOVERY FROM A SURELY FATAL DOSE OF EPINEPHRINE

Epinephrine is one of the most commonly used drugs throughout the world, and, when administered by physicians, medication with it is comparatively safe. Ordinarily recovery occurs uneventfully from rather unpleasant and sometimes alarming side-actions. Serious accidents from over-dosage would appear to be uncommon and most are probably never reported. These are more likely to occur with accidental intravenous injection than by other methods of adminisration, but little, if any, attention has been given to possible measures for relieving symptoms.

The dangers are definitely greater with lay persons, especially asthmatics using epinephrine as self-medication with a hypodermic syringe. Besides the 1:1000 solution of epinephrine hydrochloride which is available to the layman for injection there is the 1 per cent solution intended for use in vaporizers. The latter solution might be accidentally injected, or used for injection in case of unavailability of the weaker solution, and would certainly result in severe toxicity, if used in the same dosage. Thanks to the vigilance of the Council on Pharmacy and Chemistry of the American Medical Association and the Federal Food and Drug Administration the marketing of these solutions in this country is controlled by proper labeling with directions for prescriber and user. However, similar matters are poorly or not at all controlled in many other countries where there are available solutions of epinephrine 10 to 20 times stronger than the solution permitted for use as vapor in this country. A serious accident with one such solution was reported some time ago by Möller of Copenhagen. I found the report interesting and instructive, with practical suggestions which I have not seen anywhere before; and the measures seem to be successful.

The report is of the successful treatment of a child who received a surely fatal dose of epinephrine. The principle of the procedure used should be equally valuable in mitigating severe symptoms of accidental poisoning from smaller doses. The essential feature was a prompt and persistent treatment with drugs of the nitrite group. Carbaminoylcholine (doryl), a parasympathotropic stimulant used to restore the autonomic imbalance caused by the sympathetic overstimulation of the epinephrine, was ineffective. A summary of this case, therefore, is of more than passing interest.

A girl 12 years of age, body weight 34 Kg., was given subcutaneously, by accident, 20 mgm. of epinephrine (0.2 cc. of a 10 per cent spray-solution) which was double the known fatal dose for an adult man. Nausea, vomiting and a barely perceptible pulse quickly resulted; marked general paleness with coldness of extremities and increased heart rate and blood pressure were present in 20 minutes, unconsciousness in 40 minutes. Following inhalation of vapors from four ampules of amyl nitrite, consciousness was regained without change in blood pressure and heart rate. From there on, administration of the longer acting members of the nitrite group was pushed during a period of 1 hour and 40 minutes. Nitroglycerin, 3.0 mgm., was given at 1 hour and 15 minutes, then erythrol tetranitrate, 5.0 mgm. by mouth, followed by three doses of 5.0 mgm. each intravenously 10 minutes apart, followed again 15 minutes later by another 5.0 mgm. intravenously, total 25 mgm. of erythrol tetranitrate within 1 hour and 40 minutes after the accident. Three hours and 40 minutes after the epinephrine injection the facial skin was pinkish, but the legs were still cold and pale. Blood pressure was reduced and thirst marked after the third dose of erythrol tetranitrate; sweating was marked after the last dose.

The recovery of this child from twice the surely fatal adult dose of epinephrine is attributed by Möller to the persistent use of these nitrites as peripheral vasodilators, known mutual antagonists of epinephrine. Yet the peripheral vasoconstriction could not have been entirely overcome, since the paleness of the skin persisted. Other vasodilators, i.e., acetylcholine and aminophylline, have been used by others in combating epinephrine accidents, but have less to recommend them than the nitrites. According to Möller, the aim should be to overcome the marked vasoconstriction so as to improve the cerebral circulation and restore consciousness. Möller recommends giving inhalation of amyl nitrite (three drops) vapor as quickly as possible, followed by a large dose (2.0 to 4.0 mgm.) of nitroglycerin by mouth and then erythrol tetranitrate in divided doses of 5.0 mgm., to a total of 20.0 mgm., intravenously, to control the high blood pressure and promote recovery, according to individual requirements. The injection site may also be excised, if necessary.

REFERENCE

Möller, K. O.: Acta Med. Scand., 110:361, 1942, Über die Behandlung der Akuten Adrenalinvergiftung mit Bericht über einen Vergiftungsfall.

Cordially yours,

P. J. Hanzlik, M.D.,
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76th Annual Session
California Medical Association
Los Angeles
April 30—May 3, 1947

For hotel reservations, write Convention Department, Los Angeles Chamber of Commerce, 1151 South Broadway, Los Angeles, Calif.

BOOK REVIEWS

THE 1946 YEAR BOOK OF GENERAL MEDICINE. Edited by George F. Dick, M.D.; J. Burns Amberson, M.D.; George R. Minot, M.D., S.D., F.R.C.P.; William B. Castle, M.D., S.M.; William D. Stroud, M.D., and George B. Eusterman, M.D. The Year Book Publishers, Chicago. Price $3.75.

This handy pocket-sized volume contains 772 pages with good-sized print. It has a jacket upon which is printed 20 questions, given as a quiz, to stir the interest in the contents on general medicine. This yearly brief summary of important advances has been continuous since 1900.

Various professors of medical specialties have been chosen to edit the several departments of this year book. These departments are divided into (1) Infectious Diseases by George F. Dick, M.D., (2) Diseases of the Chest by J. Burns Amberson, M.D., (3) Diseases of the Blood and Blood Forming Organs; Diseases of the Kidneys, by George R. Minot, M.D., and William B. Castle, M.D., (4) Diseases of the Heart and Blood Vessels by William D. Stroud, M.D., (5) Diseases of the Digestive System and Metabolism by George B. Eusterman, M.D. Brief summaries of important advances in these fields are given. After many of the articles, the editors have commented and thus have brought the subject matter to date. Few charts and plates appear in the volume. A good informal photograph of the late Sir Thomas Lewis appears at the beginning of the Cardiac section.

The various departments have been well reviewed, and included are theoretical and practical discussions on sulfonamides, penicillin, streptomycin, folic acid, insulins, proteins and amino-acids, Rh factors, vitamins, etc., etc. It should be noted that Endocrinological Diseases are not especially reviewed in General Medicine, as a year book on Endocrinology is regularly published.

This review of General Medicine is admirably done. The editors have brought before their readers important new data, and the comments have kept the subjects alive and up-to-date. This review should be an integral part of the working library of both general practitioners and specialists in the field of medicine.

THE EYE MANIFESTATIONS OF INTERNAL DISEASES. By I. S. Tassman, M.D., Associate Professor of Ophthalmology, Graduate School of Medicine, University of Pennsylvania, Philadelphia; Attending Surgeon, Wills Hospital, Philadelphia, Pa. With 243 illustrations including 24 in color. Second Edition. 1946. The C. V. Mosby Company, St. Louis.

This book begins with the worthy presumption that ophthalmology should be considered as a branch of internal medicine and with the worthy purpose of bridging the gap which exists between the ophthalmic and the other medical aspects of internal diseases. It is regrettable that a book planned to fill such a need should be so unsatisfactory. As the book is surveyed it is seen as essentially a textbook on the eye arranged according to internal diseases. The descriptions of internal diseases allegedly follow Meakins' Practice of Medicine but the condensations are done inadequately, so that they give too little either to the internist or to the student of ophthalmology. Collaboration with an internist could have greatly improved this part of the book, which is quite a large part, and given better balance to the whole. In some conditions the eye descriptions are auxillary to those of the constitutional disease; in others the emphasis is reversed.

The index is good and helps equip the book as a compendium for reference, but the bibliography could be more complete and more up to date.

There is considerable emphasis and detail given to minor or rare conditions and too little to certain important and common ones. For instance, the entire subject of hypertension, including malignant hypertension, is covered in less than one and one-half pages of text and one black and white print. Arteriosclerosis is given two and one-half pages. On the other hand five and one-half pages are devoted to toxoplasmic encephalomyelitis.

The color photographs are good, but too few, and are usually wasted at the rate of one small print to a full page. The black and white prints are not uniformly clear. They are present in great number—and not always with apparent reason. Some would be more appropriate in a text on diseases of the skin rather than of the eye. Others are out of place: Fig. 103, a fundus demonstrating tuberous sclerosis, stares from page 236. The discussion of this subject begins on page 240 and is accompanied by two other figures. Meanwhile, the intervening pages are occupied by the text of two other conditions and prints of three. This sort of thing is confusing.

The discussions on treatment do not acknowledge the existence of penicillin, and comment on the sulfonamides is in a fashion better befitting 1938 than 1946. The comparatively few references to chemotherapy repeatedly recommend sulfanilamide, which, in general, has been discarded in favor of more effective and safer derivatives.

The final criticism is directed to a fault found all too frequently in modern American medical books, the inconstancy of the style and the English grammar.

QUARTERLY REVIEW OF OBSTETRICS AND GYNECOLOGY. Volume 1, 1943, Volume 2, 1944, Volume 3, 1945. Washington Institute of Medicine, 1720 M Street, N.W., Washington, D. C.

This collection of reviews embraces the quarterly publications of the Review of Obstetrics and Gynecology for the years 1943-45, inclusive. The publication is well edited, and the individual reviews convey the content of the various articles with considerable fidelity and without becoming stereotyped. The field seems to be very well covered, and in view of the fact that this covers war years, it is a considerable achievement. As one might expect, the foreign journals are notably lacking, with the exception of those from South America. This deficit will undoubtedly be rectified as the journals from other countries become available.

The publication is well printed; the paper is good and the binding is very satisfactory.

This presentation of the Quarterly Review of Obstetrics and Gynecology forms a valuable addition to any medical library.

SIR W. ARBUTHNOT, His Life and Work. By W. E. Tanner, M.S., F.R.C.S. The Williams and Wilkins Company, Baltimore. 1946. Price $4.50.

This is a rambling anecdotal biography written by a devoted disciple with a somewhat reverential appraisal of an admittedly very clever pioneer in surgery, many of whose contentions concerning intestinal stasis (to which subject he contributed almost a hundred articles) have not stood the test of time nor of more scientific study. However, one cannot but admire and marvel at the many-faceted character of this brilliant though sometimes erratic artist in surgery, whose Lane plates, "non-touch" method of operating for fractures, operation for lateral sinus thrombosis, administration of salt solution during operation, resection of rib for empyema, closure of cleft palate, and total colectomy blazed trails for lesser Galens to follow and later to modify or discard as newer concepts

dominated these fields. The book provides an interesting and important chapter in the history of surgery. As Rudolph Matas well said: "His name will remain permanently inscribed in history as one who made surgery better than he found it."

PENICILLIN, ITS PRACTICAL APPLICATION, under general Editorship of Sir Alexander Fleming, M.B., B.S., F.R.C.P., F.R.C.S., F.R.S., Professor of Bacteriology in the University of London; Discoverer of Penicillin; recipient of the Gold Medal for Medicine and Hygiene and the Cheadle Gold Medal, Clinical Medicine in 1908; awarded the Nobel Prize for Medicine in 1944. Cloth edition, Blakiston Company, Philadelphia, 1946; 380 pages with 59 illustrations. Price $7.00.

This book, as the name implies, attempts to collect all the present knowledge concerning penicillin with the object of applying that knowledge to practical use in the treatment of the patient.

Dr. Fleming is not the author of the book, and he, himself, has contributed only the first chapter, "History and Development of Penicillin." This chapter is interesting, well-written and as an introductory chapter establishes a good basic foundation for the specialized chapters that follow. He has invited a number of outstanding English authorities to contribute articles on the different aspects of penicillin and penicillin therapy. The book, therefore, is not a continuous text, but more of an encyclopedic résumé of our present knowledge.

The book is divided into three sections:

The first section is general and résumés and describes the chemistry and manufacture, the pharmacology, the bacteriological control of penicillin therapy and the methods of administration. This section is complete, and the student need read no further in order to apply penicillin therapy safely and correctly.

The second section is composed of articles by specialist clinicians detailing the practical use of penicillin to prophylactic use, infections, endocarditis, chest infections, chest surgery, wounds, burns, orthopedics, osteomyelitis, hand infections, abdominal infections, obstetrics and gynecology, sepsis neonatorum, brain and meningeal infections, venereal diseases, ophthalmology, otorhinolaryngology, dermatology, dental and oral infections, and in animal diseases. Each specialist has attempted to cover his entire field with treatment details for each infection or contingency. Each article repeats and emphasizes the general basic rules as set forth in the first section. Each article is complete in itself and useful to anyone who is limiting his practice to a single field. The general principles are the same as are described in the first section. Nothing new is added, except perhaps individual variations in technique and application.

The third section is a short chapter primarily for the general practitioner. The chapter is a résumé of the book, arranged similar to a quick subject reference.

This book is the most complete authentic volume ever published on the subject of penicillin. Deletion of the repetitious material and combining the specialists' articles, would have made this book outstanding. As it is, it is a valuable book for the general practitioner. It should be at hand as a reference volume in all hospitals and labraries.

It is hoped that the revised edition will be smaller, more compact and sell at a lesser cost.

MEDICAL JURISPRUDENCE

MALPRACTICE: DEGREE OF SKILL REQUIRED OF A SURGEON: ACTS CONSTITUTING NEGLIGENCE IN TREATMENT

PEART, BARATY & HASSARD, *San Francisco*

The California District Court of Appeal recently decided a case (76 A.C.A. 658) involving the degree of skill and care necessary for a surgeon to exercise and held that a physician or a surgeon is not liable for every result which may occur in medical practice, but is required only to exercise the degree of learning and skill ordinarily possessed by physicians of good standing practicing in the same locality and to use ordinary care and diligence in applying that learning and skill to the treatment of his patients.

In this case, plaintiff sued defendant for damages alleged to have resulted from malpractice on the part of defendant in the treatment of an injured arm. At the conclusion of plaintiff's case, a motion for a non-suit was granted and the plaintiff appealed therefrom.

The facts of the case upon which the plaintiff based her action for damages were as follows: Plaintiff alleged that on or about January 4, 1944, she received an injury to her right arm and thereafter employed the defendant physician to treat her injuries. Further the plaintiff contended that the defendant physician had carelessly and unskillfully operated on and treated the plaintiff's right arm, and that his negligence was the cause of permanent injury to her right shoulder, right elbow and right hand. Plaintiff alleged that defendant physician had manipulated the plaintiff's arm prior to the time when there was sufficient callous formation in the fractured elbow, and that the defendant physician had forcefully and violently manipulated plaintiff's fractured elbow beyond the point of tolerance.

At the trial there was no evidence that the defendant departed from the routine treatment in the circumstances, and there was no evidence that defendant physician failed to exercise that degree of care and skill customarily used by the profession in and about the locality where the treatment was administered. The District Court of Appeal held that the trial court was not in error when it granted the defendant's motion for a non-suit and again enunciated the rule: "The fact, if it is a fact, that the patient fails to respond to treatment, or that the results of an operation are disappointing, does not necessarily establish as a fact, the failure to exercise that degree of care and skill customarily used by the profession in and about the locality where the treatment is administered."